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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 31 1990

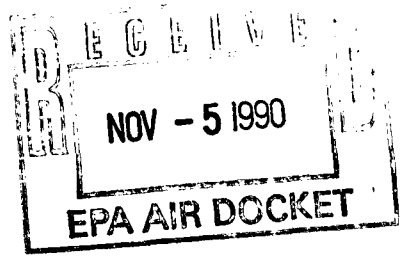
OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: ORD's Comments on the Use of Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Unleaded Gasoline

FROM: FOR Peter W. Preuss, Director
Office of Technology Transfer
and Regulatory Support (H-8105)

TO: Richard D. Wilson, Director
Office of Mobile Sources (ANR-455)



In your memoranda to me of June 13 and August 3, 1990, you requested ORD's assessment of the potential health risks associated with manganese emissions from the proposed introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) into unleaded gasoline. In addition, you requested any other comments ORD may have on the waiver application submitted to allow the use of MMT in unleaded gasoline.

The attached document presents the results of ORD's review of the health and environmental effects associated with the waiver request. (The effects associated with the potentially increased particulate emissions resulting from the addition of MMT (only recently identified) have not been addressed). There are considerable uncertainties and data gaps in the available information, which we have described in our analysis. We have provided you a separate document describing research needed to reduce these uncertainties.

In brief, it is not possible for ORD to conclude definitively that the increased use of MMT as a fuel additive will (or will not) increase public health risk. ORD's analyses show that there is the potential for a significant population to be exposed to airborne manganese levels that carry some risk of adverse health effects. Based on the existing data, however, there are many uncertainties and information gaps, some of which have also been commented on by others. Therefore, ORD believes that a discussion within the scientific community would be helpful in achieving a consensus on the uncertainties and data needed to better understand the implications of adding MMT to unleaded gasoline.

Please contact me or Stanley Durkee of my staff at 382-7669 should you desire to discuss any portion of the attached document.

Attachments

COMMENTS ON THE USE OF METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL IN UNLEADED GASOLINE

OFFICE OF RESEARCH

RESEARCH AND DEVELOPMENT

NOVEMBER 1, 1990

SUMMARY

OMS requested ORD to assist in its review of the scientific issues associated with a waiver application to add methylcyclopentadienyl manganese tricarbonyl (MMT) to unleaded gasoline. In its review, ORD considered a number of areas where the production and use of the additive could have a potential health and/or environmental impact. Potentially, humans and ecosystems could be exposed to MMT, MMT in gasoline, and their associated combustion and atmospheric and soil/groundwater transformation products. Because of time limitations, this document does not consider the recent data indicating increases in particulate emissions associated with the addition of MMT in unleaded gasoline.

ORD found that the most significant issue from this review is associated with the inhalation of Mn, particularly fine mode particulate Mn_3O_4, that results from the combustion of MMT-containing gasoline. ORD's analyses show that little risk would occur due to oral exposures resulting from the deposition of Mn-containing particles on surfaces, such as soil. However, ORD concludes that, due to inadequacies in the exposure and health data bases, it is not possible to state definitively whether a significant health risk from inhalation exposure to Mn will, (or will not) occur with usage of MMT.

ORD conducted a reasonable worst-case exposure assessment examining total exposure from a variety of microenvironments. ORD also performed a health assessment. (Note: The health effects associated with Mn exposure include neurobehavioral and reproductive dysfunction.) This assessment utilized EPA's recently verified inhalation reference concentration (RfC) for Mn, the derivation of which is discussed later in this document. The RfC is an estimate of a lifetime exposure level likely to be without appreciable adverse human health risk. ORD estimated that for a significant portion of the population, exposures would be within the uncertainty range of the RfC. ORD believes that a discussion within the scientific community would be helpful in achieving a consensus on the uncertainties and research data needed to better understand the implications of adding MMT to unleaded gasoline on the potential Mn inhalation health risk.

With regard to other issues, ORD found, based on preliminary experiments, that there is a potential for human exposure via drinking water contaminated by accidental spills/leakage of pure MMT into groundwater. However, the number of people potentially exposed is likely to be limited, since it is expected that only a few production/storage facilities will be needed to meet the demand for MMT. Inhalation exposure to MMT is not expected to result in significant risk because of MMT's rapid atmospheric degradation. Finally, ORD found that the introduction of MMT into gasoline could possibly positively affect tropospheric ozone, greenhouse

gas emissions, and various crops. Reduced vehicular emissions of aromatics due to MMT use could also reduce the cancer risk associated with benzene exposures.

This document is organized into four parts:

(1) A human health risk assessment for manganese (Mn);
(2) A limited risk assessment of MMT;
(3) A discussion of other issues that ORD has examined, including effects on ozone formation and changes in the greenhouse gas inventory; and,
(4) Eight attachments, including ORD comments on various comments provided to the docket by scientists and scientific organizations.

I. HEALTH RISK ASSESSMENT FOR MANGANESE (Mn)

A health risk assessment has several components: hazard identification, dose-response assessment, exposure assessment, and risk characterization. The first step describes the types of hazards that can be caused by Mn, such as toxicity to the central nervous system, the reproductive system, and the respiratory system, as well as Mn's essentiality as a nutrient. The dose-response characteristics of Mn are essential to estimate what levels of exposure are likely to cause certain health effects. Several approaches can be used. The oral reference dose (RfD) and inhalation reference concentration (RfC) procedures established by EPA and commonly used for non-cancer assessments were applied. The RfD/RfC is defined as an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Briefly, these procedures entail identifying a critical study, defining a no observed adverse effect level (NOAEL), and applying uncertainty and modifying factors to account for uncertainties in extrapolating from the critical study to the human population at potential risk.

The exposure assessment estimated oral and inhalation scenarios. The focus was on the inhalation scenario, which considered several microenvironments and the distribution of population exposures. The final step, risk characterization, compared the oral RfD and inhalation RfC to estimated exposures to form conclusions about the potential for adverse health risks. These components are discussed below.

Hazard Identification

Mn Toxicity

Direct quantitative comparisons of oral to inhalation exposures are not possible due to inadequacies in the data base. The dose to the target cell/molecule is the most proximate cause of toxicity. However, the relationship between the external oral or inhalation exposure to the target cell dose is complex, being determined by pharmacokinetics that will differ by route of exposure. We have not found any inhalation pharmacokinetic studies of Mn_3O_4 that quantified key elements such as lung absorption and brain target dose in humans or non-human primates after subchronic or chronic exposure. Thus, oral and inhalation exposures cannot be quantitatively compared or extrapolated at this time, requiring separate evaluations of potential oral and inhalation risks.

Manganese toxicity varies greatly among the different potential routes of exposure. When ingested, it is an essential nutrient, with a Recommended Dietary Allowance of between 2,000 and 5,000 ug/day. Overall, Mn is considered to be among the least toxic of the trace elements in mammals when ingested. In the normal adult, between 3 and 10 percent of Mn in the diet is absorbed. Total body Mn stores are regulated by a homeostatic mechanism involving absorption and excretion. Absorption of Mn can be increased in some populations (*e.g.*, pregnant women and iron-deficient individuals), and clearance mechanisms are less well-developed in fetuses and young children. More detailed health information is discussed in Attachment 1 (Health Effects of Manganese and MMT).

Manganese can be toxic when inhaled. Since the Mn emitted from vehicles will be in the fine mode particulate size range (< 2.5 μm), it is likely that most of the deposited Mn will be in the gas exchange region of the lung, where it will be readily absorbed into the blood. Once in the blood, Mn is selectively taken up by the dopamine-producing pigmented cells of the brain.

Occupational and animal studies have identified a wide array of adverse effects associated with high levels of inhaled Mn, including respiratory, neurologic, reproductive, respiratory, immunologic, and hematologic effects. Of most concern are the neurotoxic, reproductive, and respiratory effects.

Neurotoxic Effects

Neurotoxicity, especially central nervous system (CNS) damage, currently is generally accepted as the critical effect of Mn. Long-term inhalation exposure to high levels of Mn in occupational settings has long been recognized to cause a disease called manganism, which has several similarities to Parkinson's Disease.

Such overt disease, commonly called a frank effect, is preceded by a continuum of changes in the CNS, some of which have been observed at lower levels of long-term exposures of humans in occupational environments and in animal studies. The types of effects observed in occupational studies include decreased hand steadiness, impaired hand-eye coordination, slowed reaction time, impaired short-term memory, and self-reports of trembling fingers. These types of adverse effects are rather overt changes and their manifestation/detection likely reflects relatively substantial damage to, or functional impairment of, affected CNS pathways (*e.g.*, the nigro-neostriatal dopamine system of the brain found to be damaged in Parkinson's disease patients). Based on analogous experience with lead and other neurotoxic agents, there is substantial reason to believe that more subtle (and difficult to detect) neurobehavioral effects of Mn would possibly be found at lower exposure levels if more sensitive measurement techniques (*e.g.*, more rapid or complex manual performance or memory tasks) were applied.

Another key issue in Mn toxicity is the range of responsiveness in the human population. In the groups of workers studied, some showed more response than others. Children might be more responsive, based on analogy to lead toxicity, and their nervous systems may be more sensitive to a given dose compared to adults. Iron-deficient and older adults also may be susceptible subgroups. Independent of Mn, certain neurological degenerative diseases are associated with the aging process, raising the possibility that exposure to neurotoxicants could advance this process.

Reproductive Effects

The occupational exposure literature includes reports of loss of libido, impotence, and decreased numbers of children in Mn-exposed workers, raising concern about possible reproductive effects being associated with Mn and highlighting the need for better characterization of such effects, associated dose-response relationships, and underlying mechanisms of action. Currently available occupational exposure information does not permit clear delineation of either lowest observed adverse effect levels (LOAEL) or no observed adverse effect levels (NOAEL) for Mn-related reproductive effects. Decreased numbers of children have been reported for Mn-exposed workers (controlling for other factors) from exposures to Mn that were also demonstrated to be associated with neurobehavioral dysfunctions in the same workers. This raises the possibility that Mn effects on reproductive mechanisms may be occurring at essentially the same exposure levels as the above-noted Parkinson-type neurologic effects — plausibly due to Mn effects on CNS neural pathways important in neuroendocrine regulation. More extensive evaluations of Mn effects on reproductive function need to be carried out to characterize dose-response relationships and mechanisms of action. Until then, the possibility cannot be excluded of notable reproductive effects occurring at Mn exposure levels below those demonstrated thus far.

Respiratory Effects

Respiratory effects associated with inhalation exposures to Mn are also a concern. Acute exposures to very high concentrations of Mn fumes or airborne Mn particulate compounds clearly increase the incidence of pneumonia. With longer-term exposure to somewhat lower Mn concentrations more typical of occupational exposures, various respiratory symptoms and/or diseases (*e.g.*, acute and chronic bronchitis) have been reported. Also, some studies have reported evidence for small, but statistically significant, pulmonary function decrements (*e.g.*, decreased lung capacity or expiratory volume) at the same Mn exposure levels associated with the induction of Parkinson-like neurobehavioral deficits in occupationally exposed workers. The magnitude of the pulmonary effects observed, however, was not in a range to be clearly judged as adverse for the tested adult workers. What remains to be evaluated is the extent to which analogous (or other more serious) pulmonary function decrements may occur in potentially more susceptible population subgroups (*e.g.*, young children, the elderly, asthmatics, or persons with pre-existing chronic obstructive lung disease) and at what, possibly distinctly lower, Mn exposure levels such effects occur.

Dose-Response Assessment

Oral Reference Dose (RfD) for Mn

The oral reference dose (RfD) is an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The oral RfD is expressed in units of μg/kg/day. Whether doses that exceed the RfD are of concern depends not only on the extent to which the RfD is exceeded, but also on a number of factors discussed later.

EPA has identified an oral RfD of 100 μg/kg/day for the average adult, based on a composite of references identified in Attachment 1.

Inhalation Reference Concentration (RfC) for Mn

The inhalation reference concentration (RfC) is similar in concept to an oral RfD. It is an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily concentration to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It is expressed in units of $\mu g/m^3$. ORD has developed an inhalation RfC for total Mn rather than individual compounds, because the data base is inadequate to develop

an RfC for specific Mn compounds such as Mn_3O_4, the principal form of Mn in vehicle emissions. It should be recognized that the valence state of Mn affects its toxicity. Some data suggest that Mn^{3+} is more toxic than Mn^{2+} and pharmacokinetic studies show a dependence on the species of Mn used.

In developing an RfC, the literature on subchronic and chronic exposure responses is evaluated, and a critical study (or studies) is selected according to established criteria. This critical study is used as the basis for the derivation of the RfC. It is assumed that if the effects identified in the critical study are prevented, then other effects of concern will likewise be prevented. In determining the RfC, several types of uncertainty factors are used to account for uncertainties in extrapolations from the available data base to an environmental public health scenario.

On September 19, 1990, EPA's RfD/RfC Work Group verified the chronic inhalation RfC of 0.4 $\mu g/m^3$ for Mn. The principal study used to develop the RfC identified an occupational LOAEL of 970 $\mu g/m^3$ for total airborne manganese dust (Roels *et al*; 1987). In order to account for the differences between occupational and public exposure, assumed to be for 24 hours/day in accordance with the RfC methodology, an adjustment was made in dose duration, with the LOAEL being expressed as a human equilvalent concentration (HEC). This LOAEL-HEC is calculated to be 340 $\mu g/m^3$. It should be noted that a NOAEL was not identified in this or in the other occupational studies used in support of the RfC.

The Roels *et al.* study reported slowed reaction time, decreased hand steadiness, impaired eye-hand coordination, impaired short-term memory, and self-reports of trembling fingers, as well as reproductive dysfunction and pulmonary effects. The following uncertainty factors were applied to this study: (1) an uncertainty factor of 10 to account for using a LOAEL as opposed to a NOAEL; (2) a second uncertainty factor of 10 to account for sensitive populations; and (3) an additional uncertainty factor of 3 to account for the less-than-chronic exposure duration. Finally, in recognition of uncertainty associated with the exposure levels owing to the exponential increase in factory Mn production during the exposure period and the likelihood that the observed effects were related to lower prior exposure levels compared to contemporary exposure levels, an additional modifying factor of 3 was used. (EPA's standard RfD/RfC methodology provides for a modifying factor to be used to account for factors that are not routinely addressed by the methodology itself, *e.g.*, in this case, uncertainty in the exposure level associated with the reported effects.) Two other occupational studies support the Roels *et al.* (1987) study (Iregren, 1990; Chandra *et al.*, 1981). Iregren (1990) reported similar neurological effects as did Roels *et al.* (1987) in workers at a LOAEL-HEC of 90 $\mu g/m^3$. Chandra *et al.* (1981) observed neurological signs for endpoints of deep reflexes, tremors, and complaints of cough and breathing difficulties at a LOAEL-

HEC of 110 μg/m³. These findings are consistent with the body of knowledge on Mn neurotoxic effects. Although the identified LOAEL-HEC's from these studies are lower than those of Roels *et al.*, there are other study deficiencies that preclude their use as a principal study for the development of the RfC. In any case, if these two studies had been used, with their appropriate uncertainty factors, the resulting RfC would have been very close to that derived from the Roels *et al.* study.

The resulting RfC of 0.4 μg/m³ is for a 70-year lifetime exposure. Using the standard EPA assumption of 20 m³ of air breathed per day by an adult and assuming 100 percent of the Mn inhaled is absorbed into the blood, the estimated daily dose of inhaled Mn related to the RfC would be 8 μg/day. It should be noted that absorption is likely to be significantly less than 100 percent. However, in lieu of information on: the particle size fractions present in occupational versus ambient environments, specific deposition and absorption rates for these possibly different size fraction, and potentially sensitive subpopulations (*e.g.*, neonates), a uniform assumption of 100 percent is reasonable, as discussed in Attachment 1.

Another study (Nogawa *et al.*., 1973), discussed in more detail in Attachment 1, has an apparent LOAEL lower than those mentioned above. However, this study does not meet the criteria for quantitative dose-response assessment for inhalation RfC development. It should also be noted that the World Health Organization has also evaluated Mn (WHO, 1987), and has recommended a guideline value (*i.e.*, a level not anticipated to cause significant adverse health effects in sensitive subpopulations) of 1 μg/m³ (annual average).

Exposure Assessment

Direct Inhalation Exposure to Mn

ORD conducted a four-step exposure assessment associated with direct inhalation exposure to Mn. ORD's analysis recognizes there are major uncertainties in emissions, modeling, and other assumptions associated with these estimates. ORD believes that it has taken the analysis as far as it credibly can based upon the existing data.

There are considerable uncertainties in the analysis:

(1) The emissions uncertainties, discussed in more detail in Attachment 2 (Emissions and Mn Levels in Microenvironments), are significant. They include:

   (a) Insufficient data -- The Applicant measured, using the Federal Test Procedure (FTP), only nine vehicles at only one test point,

75,000 miles. Based on these tests, the Applicant reported that only 0.4 percent of the added Mn was emitted via the tailpipe; there was no accounting for the other 99.6 percent of the Mn was unaccounted for.

(b) Lack of mass balance information on the fate of Mn in fuel raises questions about Mn emissions — while the Applicant states that Mn emissions can be as much as 30 percent of the Mn added by using MMT, this leaves no accounting 70 percent. EPA's 1984 Health Assessment Document for Mn cites data indicating 15 percent to 30 percent of the Mn introduced is emitted in automobiles not equipped with catalysts. ORD believes that if Mn emissions are similar to those of lead, the percentage of Mn exhausted will both vary with the vehicle's operating condition and design, and increase whenever the vehicle accelerates from a stop or is in low speed cruise. Also, information on the measurement protocol used to collect these data is incomplete.

(2) The modeling uncertainties, discussed in Attachment 3, are also important. The model that was chosen to model microenvironment concentrations was the best available, but carries with it as much as an order of magnitude of uncertainty.

(3) Finally, important analytic assumptions, also discussed in Attachment 3, have been made. These include the activity patterns for typical urban individuals, the assumption that the distribution of Mn exposures is analogous to that of carbon monoxide, and the use of total urban U.S. population as the possible exposed population.

The first step in the analysis predicted Mn levels ($\mu g/m^3$) for "typical" and "severe" exposures in different microenvironments for varying percentages of Mn in tailpipe emissions (relative to Mn fuel content): 0.4, 10, 20, 30, 40, 60, and 100 percent. The microenvironments included home/office, personal garage, public garage, expressway, and urban street canyon scenarios. To capture the expected variability in the results stemming from different fuel economies, ORD predicted two sets of concentrations for each set of scenarios, a 20 and a 25 mile per gallon fuel economy. Attachment 2 (Emissions and Mn Levels in Microenvironments) presents the complete tables indicating $\mu g/m^3$ concentrations for each fuel economy situation and discusses the uncertainties in the emission data in detail.

ORD then used the estimates of concentration levels within each microenvironment to estimate the integrated 24-hour total exposure to a hypothetical individual (see Attachment 3, Estimates of Daily Manganese Exposure). ORD chose the example of an office worker who commutes to work to a downtown

office. (More severe but less common exposure scenarios could occur, such as those in various occupational settings, *e.g.*, toll takers, parking attendants, and highway construction workers.) ORD assumed that this hypothetical office worker starts the car in a home garage, drives on suburban and urban streets, parks in a public garage, walks to the office and reverses this cycle after work. These calculations were made assuming:

(1) a reasonable 24-hour pattern for the worker can be derived based on the limited available information on the actual activity patterns for office workers;

(2) the modeled value to be considered in each case would be the geometric mean of the "typical" and "severe" modeled concentrations;

(3) the total concentration is the sum of those due to sources within the microenvironment plus the background concentration; and,

(4) an estimate of the office worker's 24-hour accumulated dose can be obtained by multiplying the 24-hour concentration by the total amount of air breathed during the period, using the standard assumption of 20 m^3 per day.

The average dose for the hypothetical office worker was estimated to range from 0.8 to 3.4 µg/day, depending upon the tailpipe emissions assumption used (Table 1). This range is within the uncertainty bounds of the analysis. Attachment 3 provides a more detailed explanation.

Table 1. Estimated 24-hour Concentrations and Inhaled Doses for Office Worker

Percent Mn Emitted	24 Hr Concentration (µg/m^3)	24 Hour Inhaled Dose (µg)
0.4	0.04	0.8
10	0.05	1.0
20	0.07	1.3
30	0.08	1.6
40	0.09	1.8
60	0.12	2.4
100	0.17	3.4

Third, ORD estimated the distribution of doses that the exposed population might experience, since it may be assumed that all people will not receive an equivalent exposure. ORD assumed that the variability of Mn exposures was the same as that for carbon monoxide (another, more studied mobile source pollutant), and applied the results of a carbon monoxide (CO) personal monitoring study to the modeled Mn exposures. This estimate assumed the hypothetical office worker above represents the typical (50th percentile) urban individual with an "average" exposure in the general population. The rationale and limitations for this choice are contained in Attachment 3 (Estimates of Daily Manganese Exposure).

The fourth step in the analysis was to provide an estimate of the potential numbers of individuals that could possibly be exposed at or above specific 24-hour dose levels under the different scenarios (Table 2). ORD assumed:

(1) that the total urban U.S. population of 190 million people is the population at risk for exposure;

(2) the estimated total doses of 0.8 to 3.4 μg/day are at the 50 percentile of the carbon monoxide distribution in the CO monitoring study; and

(3) the distribution of exposures will be equivalent to that noted in the CO study.

While the values (rounded to one significant figure) shown in Table 2 are not absolute, they illustrate the potential range of estimated doses among segments of the population. For example, if it is assumed that 10 percent of the manganese is emitted at the tailpipe, then 50 percent of the population could receive a possible 24-hour dose of 1 μg/day or more while 0.6 percent of the population (approximately 1 million individuals) could receive a possible 24-hour dose of about 3 μg/day or more.

Indirect Exposures to Mn

In addition to direct inhalation exposure to Mn, there are other exposure possibilities. As discussed above, Mn is an essential nutrient found in many foodstuffs and also occurs in drinking water and soil. Background levels in soil can be relatively high. The key issue for consideration is whether the addition of MMT to fuels will significantly increase oral exposure to Mn above background as a result of the atmospheric deposition of Mn.

This scenario of highest interest is children, given their higher oral intake of soil. The potential importance of these exposures is illustrated by our knowledge of lead toxicity and health risk.

ORD performed an analysis to provide a conservative estimate (described in detail in Attachment 4). In this analysis, current ambient air levels of Mn were assumed to be high, 0.1 $\mu g/m^3$ (a more reasonable estimate is 0.04 $\mu g/m^3$). If the atmospheric concentrations of Mn increased from 0.1 to 1.0 $\mu g/m^3$, the concentration of Mn in soil would double in 333 years. Using assumptions for soil ingestion by children, the Mn intake in children would correspondingly increase from approximately 1.0 to 2.0 $\mu g/kg/day$. For a 10-20 kg child, this would equate to soil Mn ingestion increasing from 10-20 $\mu g/day$ to 20-40 $\mu g/day$. If the atmospheric concentration were to rise to 1.5 $\mu g/m^3$, the doubling of soil concentration and ingestion would occur in approximately 222 years. The contribution of Mn from soil contributes approximately 1 percent of the total mean daily intake of Mn from this population.

Risk Characterization for Mn

Direct Health Risks from Mn

Direct inhalation of Mn appears to be the exposure pathway that poses the greatest likelihood for human health risk. Using the exposure assessment results above, the typical human daily inhalation dose is 0.8 to 3 $\mu g/day$. In some cases (less than 1 percent of the population), these exposures may be up to an order of magnitude higher. These estimates can be compared to the daily dose associated with the inhalation RfC, 8 $\mu g/day$. It must be emphasized that the RfC is calculated for a lifetime, continuous exposure. Daily doses are discussed only to more clearly express comparisons.

The considerable uncertainty associated with both the estimates of human exposure and potential associated health effects precludes quantitative risk characterization. For example, assuming 30 percent of the Mn in MMT-containing gasoline is emitted, Table 2 shows that the distribution of exposures ranges from 1 to 8 $\mu g/day$ or greater. The daily dose calculated from the RfC, 8 $\mu g/day$, overlaps the top of this range. However, as illustrated in Figure 1, a larger overlap is present because uncertainty around both the estimated exposures and the RfC is approximately an order of magnitude. This situation of overlapping boundaries also is present at various lower level emission assumptions. For example, assuming 10 percent of the Mn is emitted, the distribution of exposures would range from 0.9 to 3 $\mu g/day$ (Figure 2). The potential nature of the risks within these boundaries is also important, and is discussed later.

There is additional uncertainty regarding the progression of effects, from an initial interaction of a toxicant (in this case, Mn) and a target cell to the manifestation of frank disease. There is no clear-cut line of adversity on such a continuum. All major organ systems, such as the central nervous system, have some reserve capacity, *i.e.*, considerable changes can occur before clinically

Table 2. Exposure Assessment Results[a]

(Estimated Daily Mn Doses in µg/day)

Percent Mn Emitted	Potentially Exposed Population (10^6)					
	160 (85%)[b]	140 (75%)	95 (50%)	50 (25%)	20 (10%)	1 (0.6%)
Current Background	.8	.8	.8	.8	.8	.8
0.4%	.8	.8	.8	.9	.9	1
10%	.9	.9	1	1	2	3
20%	1	1	1	2	2	6
30%	1	1	2	2	3	8
40%	1	1	2	3	4	10
60%	1	2	2	4	5	20
100%	2	2	3	5	8	30

a. NOTE: PROPER INTERPRETATION OF THIS CHART DEMANDS AN UNDERSTANDING OF THE UNCERTAINTIES DESCRIBED IN THE ANALYSIS

b. Percentile of population

Figure 1. Uncertainty in RfC and Exposure Estimates (assuming 30% Mn emitted)

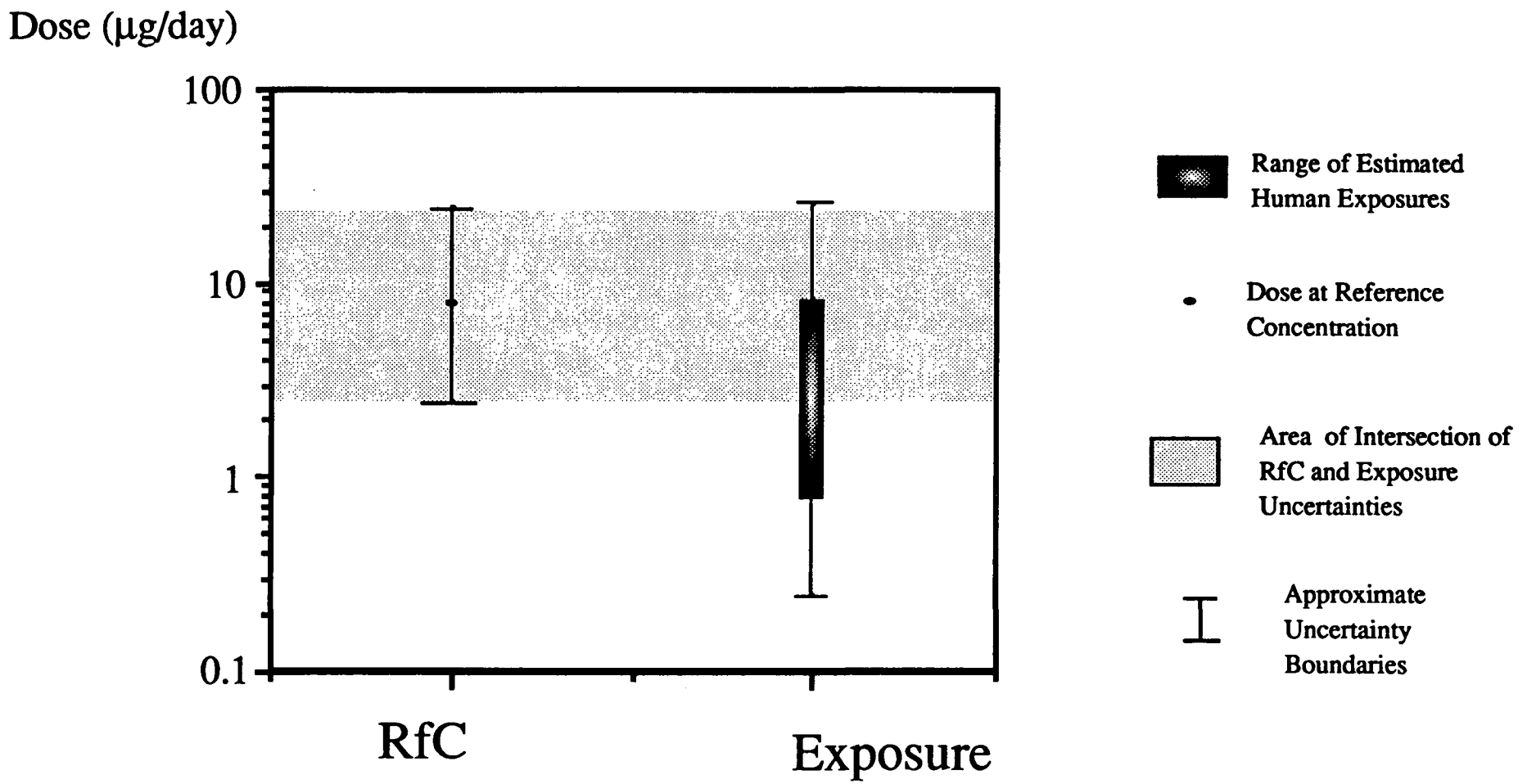
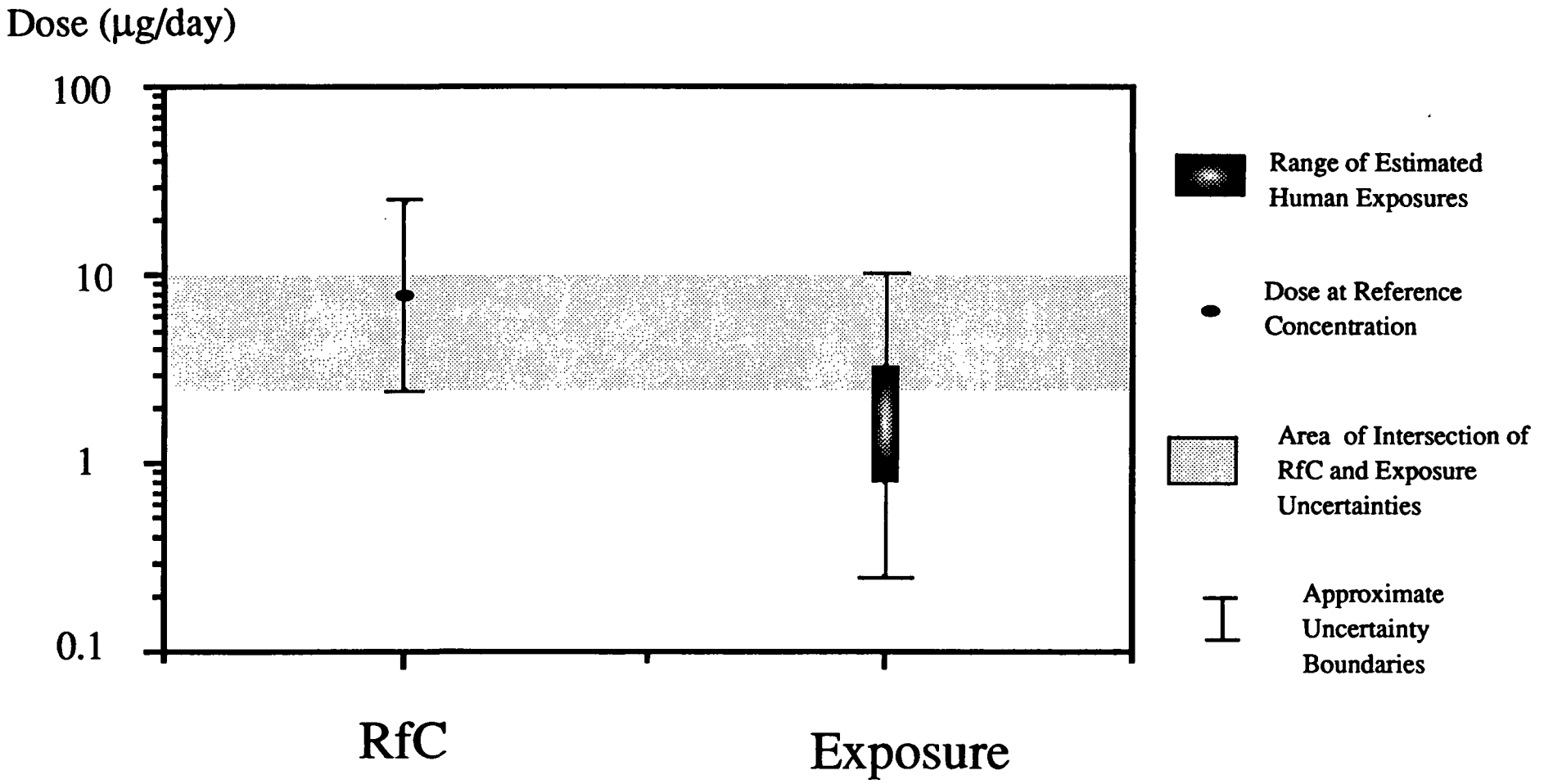


Figure 2. Uncertainty in RfC and Exposure Estimates (assuming 10% Mn emitted)



observable signs and symptoms occur. If part of that reserve function is depleted by a toxicant, an individual would then be more susceptible to the impacts of other agents or diseases affecting that organ. For example, in the case of Parkinson's disease it has been noted that overt symptoms are typically not noted until approximately 80 percent of the nigro-neostriatal dopamine system is damaged. A key issue then becomes whether increases in current Mn levels would affect reserve function.

As stated earlier, the severity of the potential health effects is also an important consideration. The effects serving as the basis of the RfC are toxicologically adverse and represent dysfunction of the central nervous system. They include impairment of short-term memory and hand-eye coordination; hand tremor; and slowing of reaction time measures. These signs and symptoms can be early indicators of neurological effects that, if they progress, can become the type of frank disease represented by manganism. The tests used in these and other more qualitative studies may not be the most sensitive indicators of general population health effects. For example, these tests also have been used to demonstrate some of the effects of lead exposure in adult workers, but when more sensitive techniques were applied to young children, neurotoxicity was observed at lower levels. From this, we conclude that the LOAELs in the occupational studies were study-specific LOAELs that might be lower if more sensitive health endpoints were studied. Also, effects such as manganism may not be fully reversible when exposure ceases. It is not known whether other neurological effects that might occur at lower exposure levels are reversible. In addition, the average exposure duration for the occupational Mn studies was approximately 10 years. Since the latency period for all the potential classes of effects is not known definitively, it is possible that with lifetime (or close to lifetime) exposure more severe effects could occur or effects could occur at lower levels than currently reported.

Another finding potentially indicative of serious health impacts concerns reproductive dysfunction. Significant reductions in fertility and increased impotence in manganese workers could signal more subtle dysfunction at lower exposure levels. More detailed hazard identification and exposure-response research is needed to evaluate this possible health risk.

Other classes of effects, such as pulmonary function decrements and increased susceptibility to infectious pulmonary disease, have also been observed after Mn exposure in occupational and population epidemiology studies. However, the studies are few; many do not permit adequate evaluation of the exposure-response relationship; and some do not meet other criteria for RfC development.

In brief, it is not possible for ORD to conclude definitively that the increased use of MMT as a fuel additive will (or will not) increase public health risk. ORD's analyses show that there is the potential for a significant population to be exposed to

airborne Mn levels that carry some risk of adverse health effects. Based on the existing data, however, there are many uncertainties and information gaps, some of which have also been commented on by others. Therefore, ORD believes that a discussion within the scientific community would be helpful in achieving a consensus on the uncertainties and research data needed to better understand the implications of adding MMT to unleaded gasoline.

Indirect Health Risks from Mn

The use of MMT is not expected to pose a significant increase in indirect health risk from Mn. Using the oral RfD as a benchmark and assuming that the background concentration of Mn increased from 0.1 μg/m to 1 μg/m^3 (an unrealistically high, conservative asumption), it would take an estimated 30,000 years of Mn accumulation in soil for soil ingestion by children to reach the oral RfD. If the concentration of Mn in air were to rise to 10 μg/m^3, it would take an estimated 3,000 years of Mn accumulation in the soil for children to be exposed to the oral RfD. In addition, the estimated increase in Mn ingestion from assumed MMT usage represents only roughly one to two percent of the total dietary intake.

II. HEALTH RISK ASSESSMENT FOR MMT

Hazard Identification

MMT Toxicity

MMT itself can readily be absorbed by humans via ingestion, inhalation or dermal contact. In these comments, only health risks associated with ingestion and dermal contact will be examined. While inhalation toxicity data for MMT are virtually nonexistent, the low vapor pressure of the compound and its rapid atmospheric decomposition (less than two minutes) result in a very low probability of appreciable exposure via this route.

Dermal exposure to liquid MMT produces a slight burning sensation. Prolonged exposure of approximately 1.5 hours produces no other untoward effects, as measured by hematology parameters, blood pressure, pulse, and muscular coordination. Unsubstantiated reports of six workers dermally exposed to MMT for 30 minutes showed signs and symptoms that included headache, nausea, gastrointestinal discomfort, breathing difficulty, chest tightness, and paraesthesia. The effects occurred within 5 minutes to 1 hour following exposure and subsided in 2 hours in four workers and persisted for 2 days in the other two. It is further reported that overexposure to MMT may affect the central nervous system and lead to convulsions, respiratory depression, cyanosis, and coma. Additional adverse effects following overexposure may include labored breathing, lethargy, lacrimation, eye inflammation, and nasal discharge.

Acute exposure of various animal species has shown that oral exposure is more toxic than dermal exposure. There are little or no data available that evaluate subchronic and chronic exposure to MMT, regardless of the route of exposure, *i.e.*, dermal, inhalation, or oral.

Exposure Assessment

Direct Exposure to MMT

In general, direct exposure to MMT may be reasonably anticipated through refueling and accidental poisoning via either ingestion or dermal contact. Given the low vapor pressure and extremely short atmospheric half life of MMT, it is considered unlikely that inhalation exposure will pose an important concern.

The scenarios of potential concern are limited to spillage or leakage of either pure MMT or MMT mixed with gasoline onto soil or into the subsurface environment from transportation accidents or storage tanks. Based on a preliminary investigation and analysis by ORD (Attachment 5), it appears that MMT is persistent in natural aquatic and soil environments, *e.g.*, subsurface environments. In the absence of light, its half-life is longer than two months. In its mixed state with gasoline, this would not be likely to result in accumulation of levels of MMT in groundwater harmful to human health. However, in its pure state, MMT could contaminate a substantial volume of groundwater, posing a potential risk to human exposure. Moreover, because pure MMT spilled or leaked into surface water would settle directly to the bottom and partition between water and the sediment, it would be persistent in anoxic bottom zones that could result in ingestion by aquatic organisms, bioaccumulation in the food chain, and possible exposure to humans as well as to the aquatic biota. However, on balance, it can be expected that there will be very few sites where large volumes of MMT are produced and stored. Thus, the population potentially exposed will likely be limited.

Risk Characterization for MMT

As mentioned above, current data are inadequate to fully assess the risks associated with the production, storage and transport of MMT. Although our analysis has shown that there is a potential for risk in ground-water and bottom sediment scenarios, consideration of these potential risks can be tempered by the facts that MMT is no more toxic than many other chemicals in use, and that the production of the quantity needed is likely to be at only a few facilities. For example, levels of MMT proposed in unleaded gasoline (1/32 grams per gallon) are low enough that for dermal or ingestion exposure, other components in gasoline are likely to result in greater risk of acute and chronic toxicity than MMT.

III. OTHER HEALTH AND ENVIRONMENTAL ISSUES EXAMINED BY ORD

A. Effects on Tropospheric Ozone

ORD has reviewed the data submitted on ozone formation and concludes that MMT in gasoline would be very unlikely to have a significant adverse effect on ozone formation. Although MMT is photochemically reactive, its presence in the gas phase would be so low that it would not affect ozone formation. Instead, the presence of MMT as a substitute for the xylenes may actually decrease photochemical ozone. A more thorough discussion is contained in Attachment 6.

B. Effects on Wildlife

Based on ORD's review of the predicted ambient air concentrations, it appears that air levels are likely to be too low to be of consequence to animals, although data are sparse on Mn effects on terrestrial wildlife. As noted above in the discussion on MMT, groundwater and bottom sediment contaminated with MMT is a potential exposure route for fish and other aquatic life. Lacking toxicity data, further characterization is not possible, except to note that such exposures would be expected to be of limited spatial and temporal distribution.

C. Effects on Crops

The impact of MMT on Mn on crops was also evaluated, since this can be a significant source of dietary Mn (see Attachment 4). Currently, several important food crops (*e.g.*, soybeans, small grains, corn) have Mn deficiencies. It is extremely difficult to predict what increases in plant concentrations of Mn would occur as a result of using MMT. It is unlikely that significant increases in Mn accumulation would occur. It is possible that a beneficial effect could occur in Mn-deficient crops.

D. Effects on Greenhouse Gas Inventory

ORD has examined this issue in the context of the data that the Applicant has provided and concludes that the changes with regard to greenhouse gas emissions are insignificant. This area was deemed worthy of investigation primarily because of the Applicant's claim that MMT use could result in a reduction in crude oil imports of about 30 million barrels per year (attributed to the reduced requirements for aromatics in gasoline). An analysis is provided in Attachment 7.

E. Effect of Aromatic Reduction

The Applicant has indicated that octane increases achieved by the introduction of MMT would result in the reduction of the use of aromatics in gasoline. Although ORD has not assessed the extent of aromatic reduction, we note

that any decrease would likely proportionately reduce the cancer risk associated with benzene from mobile sources and gasoline marketing. We note that the most recent version of OAQPS's "Six Month Study" attributes up to approximately 100 cancer deaths annually to benzene from mobile sources.

F. Comments on Docket Comments Submitted by Scientists and Scientific Organizations

ORD's comments on the docket comments submitted by scientists and scientific organizations are presented in Attachment 8.

Attachments

Attachment 1

HEALTH EFFECTS OF MANGANESE (Mn) and MMT

This attachment, prepared by ORD's Office of Health and Environmental Assessment, specifically the Environmental Criteria and Assessment Offices in Cincinnati and Research Triangle Park, provides information on the health effects of MMT and manganese.

The health effects associated with the addition of MMT to unleaded fuel need to be considered from a broad perspective that includes several potential risk pathways and several compounds.

Potential risk pathways include exposure to "pure" MMT, MMT-gasoline mixtures, and the combustion product of MMT, Mn_3O_4. As discussed in Attachment 5, it is possible that some people could be exposed to MMT in drinking water, but since MMT production and storage facilities are expected to be few, potential population exposure via drinking water is likely to be limited. Exposure to MMT-gasoline mixtures can be expected to occur with some frequency as a result of dermal exposure from spillage, use of fuel as a degreasing agent, or accidental ingestion. Such acute exposures could be associated with health effects, especially in children swallowing fuel. Although it is possible that MMT would be associated with observed toxicity, it is likely that the toxicity would be dominated by the gasoline. MMT emitted into the air will rapidly decompose, making it of negligible inhalation risk under normal usage.

Upon combustion, fine mode particles of manganese, predominantly Mn_3O_4, will be emitted from tailpipes. These particles can be inhaled into the deep lung where Mn can be absorbed into the blood and transported directly to the brain and throughout the body. Atmospheric deposition processes will result in increasing the groundwater and surface load of manganese. In terms of health risk, accumulation in soil (Attachment 4) is of interest, since children have a relatively high ingestion of soil. Thus, both oral and inhalation exposure effects of manganese require evaluation. Another key feature is that manganese is an essential element, commonly occurs in food, and is present in several vitamin/mineral supplements. The following discussion begins with dietary requirements for manganese and then is divided into sections on manganese and MMT, with emphasis on the former due to its higher human exposure potential. More extensive information is available in a Health Assessment Document for Manganese (U.S. EPA, 1984).

DIETARY Mn REQUIREMENTS AND DAILY ORAL INTAKES

Manganese has been demonstrated to be an essential trace element in every animal species tested to date. Deficiency symptoms include poor reproductive performance, growth retardation, congenital malformations in the offspring, abnormal formation of bone and cartilage, and impaired glucose tolerance (Hurley and Keen, 1987). Due to the ubiquitous distribution of manganese in edible plant materials and the relatively low requirement of mammals, a true manganese deficiency has not been adequately detailed in the human population (Underwood, 1981).

Whole grain and cereal products provide the richest sources of dietary manganese. The chemical form and nutritional bioavailability of manganese in foods is not well characterized. The Total Diet Study conducted in the U.S. between 1982 and 1986 provides mean daily dietary manganese intakes (Pennington et al., 1989). Adult men and women were found to ingest 2.7 and 2.2 mg/day, respectively. Teenage boys and girls consumed an average of 2.8 and 1.8 mg/day, respectively, while 6- to 11-month old babies and 2-year old toddlers consumed 1.1 and 1.5 mg/day, respectively.

Given the apparent lack of manganese deficiency in the human population, it is generally accepted that current dietary intakes satisfy the body requirements for manganese. Furthermore, due to the lack of adequate short-term balance studies and the complex homeostatic mechanism for manganese retention, a definitive recommended dietary allowance (RDA) has not been established. However, a provisional daily dietary manganese intake for adults has been recommended (2.0 to 5.0 mg/day) based upon current ingestion data. For infants at birth to 6-months of age and from 6-months to 1-year of age, daily dietary intakes of 0.3 to 0.6 and 0.6 to 1.0 mg/day, respectively, have been recommended. The ranges for children and adolescents are derived through extrapolation on the basis of body weight and expected food intake (NRC, 1989). In light of the remarkably steady tissue concentration of manganese in the U.S. population and the relatively low toxicity of dietary manganese, an occasional oral intake of up to 10 mg/day by adults can be considered safe.

MANGANESE

Hazard Identification

The health effects of manganese have been studied in laboratory animals and humans who received occupational and environmental exposure (U.S. EPA, 1984). Research attention has focused on populations of humans who chronically inhale large amounts of airborne manganese, *i.e.*, workers in manganese mines, steel mills,

and some chemical industries. These epidemiological studies have identified three classes of effects: neurotoxicity, reproductive toxicity, and respiratory toxicity. Generally, the state of knowledge of manganese toxicity is limited. Most human studies have not employed sensitive methods, few have been conducted at ambient or near-ambient levels, and some potentially important findings have not been fully investigated. Thus, significant uncertainty exists about some classes of effects, especially respiratory and reproductive effects.

Neurotoxicity has been the most widely evaluated endpoint. Manganese poisoning is characterized by a degeneration of neurobehavioral function resembling that of Parkinson's disease, including symptoms such as resting tremor, slowing of voluntary movements, mask-like face, and peculiar posture and gait. Other associated central nervous system effects have been measured (see following section on dose-response assessment). Another occupational finding is that workers have a higher incidence of pneumonia, presumably due to decreases in host defenses against infectious disease. Other respiratory effects include bronchitis and pulmonary function changes. Pulmonary function changes have also been reported in Japanese children living near point sources of manganese, at levels possibly as low as 4 $\mu g/m^3$ (Nogawa et al., 1973). However, there are several uncertainties about some key elements of this study, including the exposure assessment. Pulmonary effects at ambient exposure levels remain to be established.

Although few studies exist, reproductive effects are also of concern. There are reports of occupationally exposed men with impotence and fathering fewer children. Animal toxicological studies also demonstrate several types of reproductive effects, including testicular changes, at high exposure levels.

Several species of Mn oxides exist (*i.e.*, MnO_2, Mn_2O_3, Mn_3O_4), each with differences in toxicological properties. Data suggest that as the valence of Mn increases, the toxicity likewise increases (Donaldson, 1987). Also, the valence state influences the pharmacokinetics of manganese, thereby affecting toxicological properties. These issues have not been sufficiently investigated, causing uncertainties in risk assessments of manganese. For example, the pollutant of interest relative to MMT is Mn_3O_4, but the occupational literature used for the assessment involved mixtures of manganese oxides. From the information available, it is clear that Mn_3O_4 will cause effects similar to those of the mixed oxides, but given the unknown potency differences, the occupational studies may over or under estimate the potency of Mn_3O_4.

The route of manganese exposure may also influence its neurotoxicity. When inhaled as an aerosol, more of the manganese is deposited (depending on particle size) and absorbed, compared to oral exposure where up to 97% of the ingested manganese goes unabsorbed. Manganese from MMT-containing gasoline

is emitted primarily as Mn_3O_4 particles ranging in size from 0.2 to 0.4 μm. Thus, deposition in the gas-exchange region of the lung is expected, facilitating absorption into the blood. Also, once accumulated in the lungs, manganese is released gradually over time, further extending the period of target site exposure and susceptibility to development of health effects. This may explain the early onset and prolonged effects of manganese toxicity following inhalation exposure. The dopamine-rich nigrostriatal tract of the brain is considered to be the primary target tissue of Mn outside the respiratory tract. This region of the brain is related to Parkinson's disease and may also be involved in the mechanisms of the observed reproductive toxicity.

There are no quantitative data on the inhalation absorption rates of the different manganese compounds (U.S. EPA, 1984). Mena et al. (1969) observed no difference between the absorption of 1 μm particles of $MnCl_2$ and Mn_2O_3. However, following intratracheal instillation of $MnCl_2$ and Mn_3O_4, the chloride cleared four times faster than the oxide from the lung (Drown et al., 1986). In general, lung clearance is faster for chemicals with greater water solubility. The potential for lung toxicity typically is less for chemicals with a faster lung clearance. However, water solubility cannot always predict lung clearance, since cellular mechanisms can remove relatively insoluble particles from the lung as rapidly as chemical dissolution and absorption. Faster brain manganese elimination half-times have been reported in monkeys exposed to manganese via intravenous or subcutaneous injection (Newland et al., 1987). It is suggested that the slower rates of decline in brain manganese following inhalation probably reflects replenishment from manganese deposited in other organs, particularly the lungs.

Overall, manganese is considered to be among the least toxic of the trace elements in mammals when ingested. However, there is some indication that manganese in infant formulas may be a factor in contributing to learning disabilities in hyperactive children, although the database is sketchy and requires additional confirmation (Collip et al., 1983).

It is of interest to compare oral and inhalation exposure to Mn since oral exposure generally causes no toxicity in humans, whereas sufficient occupational exposure via inhalation causes effects. Toxicity is determined by the dose of the toxicant to the target site, which actually is likely to be at the molecular level but is more often measured at the organ level. The dose to the target site is dependent on a complex series of events, beginning with exposure, and including pharmacokinetic processes such as deposition, absorption, distribution and clearance. Thus, the route of exposure becomes important insofar as there are pharmacokinetic differences. For example, an oral "external" exposure to 100 μg of a chemical would not be likely to result in toxicity equivalent to an inhalation "external" exposure to 100 μg of that toxicant; on the other hand, a 10 μg dose to the

target cell resulting from oral exposure would be quite likely to have the same effect as a 10 μg target cell dose resulting from inhalation exposure. (For further discussion of issues relating to exposure routes, see page 13.)

These principles can be applied to Mn, but unfortunately serious inadequacies in the data base preclude quantitative oral-to-inhalation comparisons. An adequate data base would include data comparing exposure levels to target site dosage collected in humans or animal species (*e.g.*, monkeys) having great similarities in the target site. The data would be based on chronic oral and inhalation exposures to levels and forms of Mn typically encountered by the population. For example, we know that the form of Mn (*e.g.*, $MnCl_2$, MnO_2, Mn_3O_4) has an important influence on pharmacokinetics (EPA, 1984), as does the level of Mn (Wieczorek and Oberdorster, 1989). In rats acutely exposed to two levels of $MnCl_2$ (2.93 mg Mn/m^3 and 129 mg Mn/m^3), brain levels of Mn were higher as a result of slower clearance in the rats exposed to 2.93 mg/m^3 (Wieczorek and Oberdorster, 1989). Also, the length of exposure is important. When clearance of Mn was measured in healthy subjects, healthy Mn miners, and miners removed form Mn exposure due to chronic Mn poisoning, clearance (as total body turnover) differed, being 37.5, 15, and 28 days, respectively (EPA, 1984). Knowing how age influences pharmacokinetics of Mn would also be crucial. For example, data from acute oral exposures in animals indicate that infant rats had more Mn in the brain than did adolescent or adult rats (Cahill et al., 1980).

DOSE-RESPONSE ASSESSMENT

Oral Reference Dose and Inhalation Reference Concentration

Empirical observation generally reveals that as the dosage of a toxicant is increased, the toxic response also increases. In general, this increase occurs in severity, intensity, and percentage of population responding. Dose-response assessment involves the quantitative evaluation of the toxicity data available for a chemical that has been evaluated in the hazard identification step in terms of the nature and quality of the studies, the relevance of the experimental routes of exposure, and the nature and significance to human health of the observed effects. There are several approaches to developing a dose-response assessment. The one applied to Mn is the use of the oral reference dose (RfD) and the inhalation reference concentration (RfC). The RfD and RfC are estimates, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population (including sensitive subgroups) that are likely to be without an appreciable risk of deleterious effects during a lifetime. Both RfDs and RfCs are developed by EPA using methods described in more detail elsewhere (U.S. EPA,

1990a; Barnes and Dourson, 1988), and are subject to internal EPA review by the EPA RfD/RfC Work Group. Once a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) has been determined for a data set based on a particular principal study, the RfD and RfC can be calculated by application of uncertainty factors (UF) to address uncertainties in extrapolations performed to establish the human health risk estimate. The RfD/RfC is determined by use of the following equation, with appropriate modifications to account for inherent differences between the RfD and RfC:

$$\text{RfD or RfC} = \text{NOAEL}/(\text{UF} \times \text{MF}).$$

where:

NOAEL = no observed adverse effect level
UF = uncertainty factor
MF = modifying factor

The RfD/RfC is useful as a reference point for gauging the potential effects of other doses. Doses at the RfD/RfC or less are not likely to be associated with any significant health risks, and are therefore likely to be protective and of little health concern. In contrast, as the amount and frequency of exposures exceeding the RfD/RfC increase, the probability that adverse effects may be observed in a human population also increases. Moreover, the precision of the RfD/RfC depends in part on the overall magnitude of the composite uncertainty and modifying factors used in its calculation. The precision at best is probably one significant figure and more generally an order of magnitude. As the magnitude of this composite factor increases, the RfD/RfC estimate becomes even less accurate. The determination of an RfD/RfC requires scientific judgments as to the appropriate NOAEL or LOAEL and uncertainty and/or modifying factors.

As noted above, the inhalation RfC is defined in the same way as the oral RfD, but is expressed in units of $\mu g/m^3$ and not as mg/kg/day. Furthermore, the interim inhalation methodology used to derive the RfC accounts for dosimetric adjustments to address the dynamics of the respiratory system as the portal of entry and its interaction with various types of agents (particles or gases) (U.S. EPA, 1990a). Therefore, the size and size distribution of the particle inhaled, the specific site affected by the agent, and the duration of exposure in both experimental animals and humans are taken into consideration when calculating the RfC. The NOAEL or LOAEL values from the studies of interest are adjusted to a NOAEL(HEC) or LOAEL (HEC) (HEC = human equivalent concentration), which is used to operationally derive the RfC. For example, when human occupational data presented as time-weighted averages are used to derive the RfC (as was done with Mn), the occupational exposure level was assumed to have a duration of 8 hr/day for 5 days/week. The RfC describes a human lifetime (70 years) of continuous (24

hour/day) exposure. Thus, occupational exposure is adjusted to a continuous exposure to determine the HEC, using the formula:

$$\text{LOAEL or NOAEL(HEC)} = \text{exp. LOAEL or NOAEL } (\mu g/m^3) \times 10\ m^3 / 20\ m^3 \text{ exp. days per week} / 7$$

where:

exp. = experimental regimen

$10\ m^3 / 20\ m^3$ = ratio of assumed breathing volume during a workday to volume of an average individual during an entire day

Oral RfD

An RfD for chronic oral exposure was established and verified for manganese in June, 1990. The establishment of the NOAEL of 10 mg/day (0.14 mg/kg/day for a 70 kg adult) for manganese is based on a composite of data from three references. The World Health Organization (1973) reported no adverse effects in humans consuming supplements of 8-9 mg Mn/day (0.11-0.13 mg/kg/day). Schroeder et al. (1966) reported a chronic human NOAEL of 11.5 mg Mn/day (0.16 mg/kg/day). The National Research Council (1989) determined "safe and adequate" levels to be 2-5 mg Mn/day for adults (0.03-0.07 mg/kg/day), with an upper limit of "safe" intake of 10 mg/day. Given the nature of the data base, it was unnecessary to apply uncertainty and modifying factors. This resulted in an RfD of 0.1 mg/kg/day.

Inhalation RfC

The inhalation RfC of 0.4 $\mu g/m^3$ for Mn was verified at the September 19, 1990 EPA RfD/RfC Work Group meeting. Several occupational exposure and animal inhalation studies exist. The use of rodents to establish inhalation effect levels for neurotoxicological effects in humans may be questioned since Mn accumulates primarily in pigmented tissue of the brain and rodents are void of pigmented tissue in the striatum, and the duplication of the neurotoxic effects has not been established for the rodent. Therefore, the best data set available to establish an inhalation RfC is from occupational studies. Roels et al. (1987) was selected as the principal study to develop the inhalation RfC.

An identified LOAEL-HEC that is corrected for an occupational exposure scenario in the Roels et al. study is 340 $\mu g/m^3$. A composite uncertainty factor of 300 is used to account for: (1) the use of a LOAEL (rather than a NOAEL), (2) sensitive individuals, and (3) uncertainty regarding bioaccumulation and the lack of chronic exposure durations in the chosen studies. An additional modifying factor of 3 is used to account for the exponential increase in Mn usage at the factory during the

exposure period and the resultant increase in ambient factory Mn levels during the monitoring period.

The Roels et al. study, as well as the supporting studies, indicated exposure levels associated with effects (assumed to be a LOAEL) and did not establish exposure levels having no effects (*i.e.*, NOAEL). Since the RfC seeks a "safe" level, its derivation is based on a NOAEL. This makes it necessary to use an uncertainty factor for the Roels et al. LOAEL-HEC to extrapolate to an assumed NOAEL-HEC; a factor of 10 was chosen based on the RfC methodology (U.S. EPA, 1990a). The workers in the principal study are not representative of the potential range of susceptibility of the exposed public. For example, children and the elderly may have an enhanced susceptibility to Mn. Therefore, an uncertainty factor of 10 was used, according to the RfC methodology, to account for potential sensitive subpopulations in the general public. Also, the workers in the Roels et al. study had a less-than-lifetime exposure, requiring extrapolation to a lifetime exposure for the general public. An uncertainty factor of 3 was applied to account for this difference. Finally, a modifying factor of 3 was used to account for the uncertainty in the reported exposure level in the Roels et al. study. Application of the uncertainty and modifying factors yields a final RfC for Mn of 0.4 $\mu g/m^3$. In addition, the RfD/RfC Work Group assigns a confidence rating to the quality of the critical study used for derivation of the RfC and the supporting data base. A confidence rating is also assigned to the RfC, reflecting the ratings assigned to the study and the data base. For the Mn RfC, the confidence rating was "medium" for all these elements.

There are several deficiencies with the Roels et al. study, such as the proper matching of exposed and control groups, particularly with respect to parameters that influence pulmonary function testing and psychomotor function; the methodology of sampling used to measure the lung ventilatory parameters; the duration of exposure (range 1-19 years, mean 7.1); and the actual concentration and particle size of manganese during the exposure period. The use of the Roels et al. study to develop the RfC is supported by two other occupational studies that report similar neurological effects at levels near that reported by Roels et al. (Iregren, 1990; Chandra et al., 1981). Although both Iregren (LOAEL-HEC= 90 $\mu g/m^3$) and Chandra et al. (LOAEL-HEC= 110 $\mu g/m^3$) report effect levels lower than that of Roels et al., there are deficiencies respective to each of those reports that preclude their use as the principal study in the RfC development (see below). If these studies had been used, a composite uncertainty factor on the order of 300 would likely have been applied, resulting in RfC's very close to the one derived from the Roels et al. study. It is the opinion of the RfC Work Group that the best available data on which to base the RfC is found in the Roels et al. study with a modifying factor to account for exposure uncertainty. Without the supporting evidence of Iregren and Chandra et al., it would not have been possible to derive an RfC based solely on Roels et al. (1987).

Key Health Issues in Studies Supporting the RfC

In comparing the study by Roels et al. (1987) to that of Chandra et al. (1981), the Roels et al. study appears to be more reliable than the Chandra et al. study as a basis for the RfC. The Chandra et al. (1981) report provides no information on the methods employed to collect data. Although significant effects are reported for "deep reflexes" and "tremors", which are qualitatively consistent with the typical neurotoxic effects of manganese, it appears that these endpoints were assessed through a non-blind neurological examination. If in fact the examiner was aware of a subject's exposure condition, then the results are questionable. One may also question the sensitivity of a clinical neurological examination for detecting what could be quite subtle neurotoxic effects. Certainly, the literature on lead neurotoxicity indicates that such exams are relatively insensitive. In sum, although the findings of Chandra et al. (1981) may be viewed as supportive of other study findings, they cannot be relied upon as the primary basis for assessing the health risks of manganese.

The study by Roels et al. (1987) provides evidence of neurobehavioral impairment qualitatively consistent with the tremor that is generally considered a classic sign of frank manganese neurotoxicity. Specifically, the Roels et al. (1987) findings of concentration-related impairments in hand steadiness and eye-hand coordination, along with statistically significant slowing and increased variability of mean reaction time measures, are indicative of central nervous system (CNS) dysfunction involving motor control. These results are secondarily supported by a significantly greater prevalence of self-reported trembling of fingers in the manganese-exposed workers versus matched control workers. In addition, the impairment of short-term memory found in this study is also indicative of CNS dysfunction and is consistent with clinical reports of memory impairment at higher exposure levels.

Concentration-response analyses in the Roels et al. study compared blood manganese levels (0, <1, 1-1.5, and >1.5 μg/dl) to eye-hand coordination measures, hand steadiness, and serum calcium levels; all blood levels were statistically significant by a chi-square test. Short-term memory performance was related to exposure duration (0, <3, 3-9, and >9 years of manganese exposure) rather than blood levels; this relationship appeared to be exposure-related but failed to achieve statistical significance at $p = 0.05$. As presented by the authors, none of these relationships showed any evident threshold, except for the eye-hand coordination measures. However, it is possible that even the J-shaped relationships found for these measures (*i.e.*, where the <1 μg/dl group performed better than the controls) could reflect a neurological perturbation that is not necessarily benign (see discussion of paradoxical dose-response curves in Davis and Svendsgaard, 1990). The lack of an apparent threshold in these analyses does not establish that no

threshold exists, but it does suggest that caution should be exercised in determining an allowable chronic exposure level.

To help evaluate some of the uncertainties associated with the Roels et al. study and their implications for assessing the potential health risks of manganese, it may be useful to compare their results on manganese neurotoxicity with the much more extensive information on lead neurotoxicity. For example, several studies of neurobehavioral function in lead workers indicate that, with the exception of nerve conduction velocity, neurobehavioral effects in adult workers generally begin to occur at blood lead levels of 40 μg/dl and higher (U.S. EPA, 1986). Neurobehavioral effects in children, on the other hand, have been well established at blood lead levels of 10-15 μg/dl and possibly lower (U.S. EPA, 1986, 1990b; ATSDR, 1988; Davis and Svendsgaard, 1987). If this comparison of LOAELs for lead neurotoxicity in adults and children is used as a guide to assessing manganese neurotoxicity, it is possible that children could experience neurotoxic effects of manganese exposure at much lower levels than adults. Note that this potentially greater sensitivity of children is independent of (and in addition to) the greater absorption and retention of manganese following oral exposure in young versus adult organisms. At the other end of the age spectrum, elderly adults may also constitute a sensitive subpopulation, by comparison to adults of working age. Furthermore, as in the case of lead, large individual differences — independent of age — are evident for manganese uptake and toxicity. Thus, there is reason to believe that use of a 10-fold uncertainty factor for sensitive individuals is warranted.

In assessing the potential health risks of manganese, allowance should also be made for another feature of the Roels et al. study. Although no monitoring data were available to characterize past exposure levels in this population, company data indicated that manganese dioxide production had increased greatly between 1965 (440 metric tons) and 1981 (22,000 mt), with no industrial hygiene-significant changes in production processes since the plant opened in 1964. Thus, measurements of airborne manganese taken at the time of this study may have been much higher than the levels to which the workers had been exposed over much of their work history. Since the mean job tenure of the manganese workers was 7.1 years (range of 1-19 years), some adjustment of an effect level that might be derived from this study seems appropriate. Based on the production data provided in the Roels report, a correction factor would appear reasonable. In addition, some adjustment for lifetime exposure (versus an average of only 7.1 years), was considered and a modifying factor of 3 was applied.

Assessing the effects of "lifetime exposure" takes on some special significance when subtle neurobehavioral effects are involved. There has been increasing interest within the field of neurotoxicology about the phenomenon of accelerated neuronal attrition and/or aging due to much earlier low-level exposure to a

neurotoxic agent. The concern is that an initial subclinical insult may not be evident until several decades later. Thus, a study that evaluates neurobehavorial performance only 7 years after the onset of exposure (on average) may not have allowed enough lag time to detect long-term sequelae. Clearly, the uncertainty associated with evaluating the effects of Mn after less than one decade of exposure, on average, should be explicitly noted when assessing the potential health risks of lifetime exposure to Mn.

Although the study by Roels et al. appears to be adequate in design and execution to derive information for health risk assessment purposes, certain limitations should be noted. One shortcoming is the lack of adjustment for age of subject in the psychomotor measures. Age-standardization was used in the short-term memory task, but not in the measures of reaction time and tremor (hand steadiness and eye-hand coordination). Since the mean age of the control group was higher than that of the exposed group, the likely effect of a lack of age-adjustment was to underestimate the effect of manganese. Another limitation of the Roels et al. study was the lack of correction for multiple tests. Differences between control and exposed groups on several neurobehavioral measures were assessed with simple t tests or chi-square tests. With $\alpha = 0.05$, one in twenty such tests could be found statistically significant by chance alone. However, it appears that this percentage was well exceeded, *e.g.*, 5 of 8 reaction time measures were significant and 7 of 11 short-term memory measures were significant. Thus, these flaws in the Roels et al. study do not appear to compromise its utility for risk assessment purposes.

Another recent report on neurobehavioral effects in Mn-exposed workers has become available (Iregren, 1990 in press). The exposure levels monitored at the time of the Iregren study ranged from 20 to 1400 $\mu g/m^3$, with a mean of 250 and a median of 140 $\mu g/m^3$. Data from earlier monitoring of the factories involved indicated "essentially no changes in the exposure levels for the past 17 or 18 years, respectively." The duration of workers' exposure ranged from 1 to 35 years, with a mean of 9.9 and a median of 2.6 years. Iregren used a battery of 10 tests (8 of which were computerized and, therefore, automated in administration) to evaluate neurobehavioral function in 30 Mn workers and 60 matched controls. Two-way analyses of variance indicated significant differences between exposed and reference groups on tests of simple reaction time, digit span (a short term memory test), finger tapping (speed as well as endurance), and mental additions and verbal ability. Since the last two results suggest that the groups were not matched for general cognitive abilities, additional matching based on the verbal test scores was used to compare the groups. This additional criterion reduced the reference group to 30 subjects. In these comparisons, simple reaction time and the standard deviation of reaction time, along with finger tapping speed of the dominant hand, were significantly different. Iregren also analyzed the full data set by analysis of covariance, using

verbal test scores as a covariate, and found that the neurobehavioral differences between the two groups remained statistically significant.

The Iregren study supports the findings of Roels et al. (1987). Unlike the Roels study, no information on exposure to other pollutants is presented, and so the possibility of confounding exposures exists in the Iregren study. It shares with the Roels study the weakness of multiple statistical comparisons, although the number of significant results is great enough to discount concerns about chance findings. Also, the specific findings that achieved statistical significance, especially slowed and increased variability and reaction time, make it unlikely that the results were due to chance. One advantage of the Iregren study over that of the Roels study is that exposure levels were apparently more uniform. Clearly, the two reports support one another and provide a consistent pattern of evidence of neurobehavorial effects of low-level occupational Mn exposure.

Another finding reported by Roels et al., in both the subject 1987 report and in a separate 1985 report (Lauwerys et al., 1985), concerns reproductive function in this population of manganese workers. Compared to controls, the manganese-exposed workers had significantly fewer children during the period of their exposure. Also, six of eight-five manganese workers reported impotence whereas none of the control workers experienced impotence. Studies of manganese toxicity in rabbits, mice, and rats have shown testicular changes, retarded sexual development, and other reproductive effects (U.S. EPA, 1984). Although much remains to be learned about the mechanisms underlying these effects, some information on neurotoxic effects of manganese suggests the possibility of a common or related mechanism. Several lines of evidence from experimental animal studies and human postmortem results indicate that dopamine pathways are disrupted by manganese exposure. Impaired dopaminergic mechanisms may not only account for the commonly observed neurobehavioral effects of manganese but, potentially, may contribute to effects on hypothalamic receptors involved in regulating various hormones and hormonal releasing and inhibiting factors associated with reproductive function. Although the reproductive effects of manganese toxicity are not as well characterized as the neurobehavioral effects, they could constitute potentially quite serious health effects that clearly merit further study.

An increased incidence of pneumonia and other respiratory effects (bronchitis, increased incidence of colds, pulmonary function changes) have been reported in individuals exposed occupationally to airborne manganese (Roels et al., 1987; Chandra et al., 1981). An increase in respiratory symptoms and decrease in pulmonary functions has also been reported in students living near a ferromanganese manufacturing plant; Mn levels were estimated to be 4 $\mu m/m^3$ 100 km away from the plant (Nogawa et al., 1973). Although Nogawa et al. reported effects at low levels, they did not control for socioeconomic variables, measure manganese levels within the schools, or adequately evaluate exposure (*e.g.*, other

heavy metals or particulate matter). Thus, this study did not meet the criteria for RfC development, although it is of interest since various classes of respiratory effects (lung structural damage and pneumonia) have also been reported in humans and animals (Lloyd-Davies, 1946; Suzuki et al., 1978; Nishiyama et al., 1975; Shiotsuka, 1984; Ulrich et al., 1979.) It is unlikely that exposure to manganese is solely responsible for the increase in the prevalence of pneumonia, bronchitis, coughs, and cold observed in human and animal studies. Rather, it is likely that manganese exposure results in an increased susceptibility to infection. This is supported by several immunotoxicity studies in animals and other studies in which increased mortality occurred in manganese-exposed animals exposed to bacteria (U.S. EPA, 1984).

The fact that other effects were noted by Roels et al. in their study, namely reproductive and respiratory effects, suggests that additional caution is warranted in assessing the public health implications of these findings. Although protecting against neurotoxic effects may provide adequate protection against reproductive and pulmonary toxicity in this case, the presence of these other potential health effects should yield a more protective stance than would be justified by evidence of only one critical effect.

It is evident that more information is needed to adequately assess the potential health risks associated with low-level manganese exposure. In particular, more detailed exposure-response studies are needed for the assessment of low-level neurotoxic effects, and basic hazard identification and exposure-response data are needed for reproductive and respiratory effects. Given the possibility of a common or related neurochemical/neuropathological mechanism affecting both neurobehavioral and reproductive functions, attention should also be devoted to mechanistic studies as a means of assisting the interpretation of these effects and their seriousness.

Dosimetric Issues Related to the RfC

As discussed above, the RfC methodology as applied to human occupational studies, contains an adjustment to account for the difference between the assumed 8-hour/day occupational exposure and the assumed 24-hour/day public exposure. For such human studies, the methodology is based on the exposure (in the case of manganese, the LOAEL-HEC), not the dose that would likely be delivered to the respiratory system, blood, or target tissues because in many instances, including manganese, the data base does not permit such precision. However, it is the target site dose that is the proximate cause of toxicity. Thus, it would be of interest to be able to relate the precise dose of the RfC critical study (and hence the precise dose supporting the RfC derivation) to the precise dose the population would receive under ambient conditions, which are likely to be

different from those of the critical study. Given the data base on manganese, which lacks adequate pharmacokinetic data, such quantitative analyses cannot be performed. Nevertheless, the issue can be discussed, illustrating the basis of assumptions that can be used in subsequent risk characterizations. In this discussion, we will consider both respiratory tract deposition and subsequent absorption into the blood.

As a basic principle, particles are deposited in the three regions of the respiratory tract (extrathoracic, tracheobronchial, and pulmonary) as a function of particle size. Those particles depositing in the extrathoracic and tracheobronchial regions are predominantly cleared by the mucociliary escalator into the gastrointestinal tract where absorption will be quite low (about 3 percent). For manganese, another possibility exists. A brief report (Perl and Good, 1987) suggested that another heavy metal, aluminum, was directly transported to the brain via nasal olfactory pathways (*i.e.*, from extrathoracic deposition). One could speculate that this pathway may operate for manganese, raising additional difficulty in understanding target site dosage. Particles deposited in the pulmonary region will be cleared predominantly by absorption into systemic compartment via the blood and lymph of the pulmonary circulation. From all of these factors, we assume 100 percent absorption of particles deposited in the pulmonary region, recognizing that this ignores other mechanisms that are likely to occur to some unquantified degree.

Deposition, absorption, and distribution of Mn is likely to vary among the population. For example, neonates and children may have differences in deposition and absorption. Iron deficiency, acting through mechanisms of transferrin transport, may result in an increase in Mn uptake to the brain (Aschner and Aschner, 1990). It should also be noted that respiratory tract clearance of metal oxides is generally slower than that of chlorides. Thus, the lung may act as a reservoir for Mn, resulting in a duration of dosage to the target site that is longer than the exposure, *per se*.

Applying the principles in the background above to the likely dosimetry and absorption that occurred in the Roels et al. study is quantitatively impossible, since no particle sizes were given. Given the nature of the manufacturing process, we may assume that the particle sizes were in the coarse mode, but for the sake of the discussion, let us consider an even wider range and make calculations for particle sizes of 0.2 μm, 2 μm, and 10 μm. It was also assumed that the particles were monodisperse, which they certainly were not. For example, it is likely that a range of sizes existed. Humans at rest breathing oronasally will have a pulmonary deposition of about 7 percent, 18 percent, and 5 percent for monodisperse particles of 0.2 μm, 2 μm, and 10 μm, respectively (Jarabek et al., 1989). Using the LOAEL-HEC of the Roels et al. study (340 μg/m3) and the standard assumption of a ventilatory volume of 20 m^3/day, and considering the pulmonary regional deposition fraction, the calculated mass deposited in the pulmonary region would be about 460 μg, 1200

μg, and 340 μg for 0.2 μm, 2 μm, and 10 μm particles, respectively. These would be assumed LOAEL-associated doses. Taking these doses and dividing by 900 (the combination of uncertainty and modifying factors used for the RfC derivation) result in about 0.5 μg, 1.3 μg, and 0.4 μg deposited at the RfC level for 0.2 μm, 2 μm, and 10 μm particles, respectively.

These calculations can also be applied to the assumed exposures to Mn_3O_4 resulting from MMT vehicular use, having particle sizes thought to be 0.2 to 0.4 μm. Pulmonary regional deposition of these particles is estimated to be 7 - 10 percent (Jarabek et al., 1989). Using the RfC of 0.4 $\mu g/m^3$ with the standard assumption of 20 m^3 of air breathed per day, 7-10 percent deposition would result in 0.6 - 0.8 μg deposited in the pulmonary region per day.

It must be emphasized that given all the assumptions involved, there are very major uncertainties in any comparisons. Such comparisons suggest that the potential range of doses associated with the RfC-Roels data (0.4 to 1.3 μg/day) are not substantially different from the potential range of doses associated with the "generic" Mn RfC (0.6 - 0.8 μg/day). Difficulties in comparisons are further compounded when we consider that the Roels et al. study involved mixed Mn oxides (with substantial MnO_2), while the public exposure of concern is Mn_3O_4. Thus, even if the dosimetry calculations above were precise, the absorption and perhaps distribution and brain uptake would have a dependence on the species of oxide. Under all of these circumstances, it is reasonable to use a simplifying assumption. When considering the dose associated with the Mn RfC, we assume 100 percent absorption and 20 m^3 breathed per day, *i.e.* a daily dose of 0.8 μg/day. This is not an absolutely correct number, but as has been discussed, any differences between this number and the "real" number for public exposure to Mn_3O_4 is not likely to be extremely large.

In any case, the absorbed doses estimated above are not identical to the target site doses, although there is an unmeasured relationship. Until the data specified above become available, we are left with the conclusion that certain inhalation exposures, such as those in the occupational studies, cause adverse effects, and the no observed adverse effect level (NOAEL) for humans has not been experimentally defined. Views could differ on what constitutes a NOAEL and a relatively "safe" level which would consider the range of susceptibilities in the general populace. ORD applied EPA's inhalation reference concentration (RfC) methodology to the occupational inhalation exposure literature by, generally, extrapolating "downward" to an inhalation exposure thought to be without appreciable risk of adverse effects. The RfC is not intended to be an absolutely accurate value; as stated elsewhere, it is encompassed by an order of magnitude uncertainty. Nevertheless, it is based on inhalation data. To take oral no-effect exposure levels and extrapolate to inhalation

levels, without knowing quantitative pharmacokinetic relationships between oral and inhalation exposures, has less scientific validity.

MMT

The available data on MMT suggest that MMT in gasoline is photolabile and rapidly decomposes in the presence of both light and oxygen. Upon degradation, the manganese component is converted to a mixture of solid manganese oxides and carbonates, and the organic moiety converts to a complex mixture of acids, esters, and hydrocarbon polymers.

Exposure to MMT vapors produces a metallic taste when inhaled. Dermal exposure to liquid MMT produces a slight burning sensation. Prolonged exposure of approximately 1.5 hours produces no other untoward effects as measured by hematology parameters, blood pressure, pulse, and muscular coordination (Ethyl Corporation, 1977). Unsubstantiated reports of six workers dermally exposed to MMT for 30 minutes indicated signs and symptoms that included headache, nausea, gastrointestinal discomfort, dyspnea, chest tightness and paraesthesia. The effects occurred within 5 minutes to 1 hour following exposure and subsided in 2 hours in four workers and persisted for 2 days in the other two. It is further reported (Ethyl Corporation, 1976) that overexposure to MMT may affect the central nervous system and lead to convulsions, respiratory depression, cyanosis, and coma. Additional adverse effects following overexposure may include labored breathing, lethargy, lacrimation, eye inflammation, and nasal discharge. No overexposures to MMT resulting in lethality to humans have been reported.

Various animal toxicity studies have shown that species differ in their sensitivity to MMT, that female rats are more sensitive than male rats, and that oral exposure is more toxic than is dermal exposure (Hakkinen and Haschek, 1982; Hinderer, 1979; NAS, 1973). There are scant or no data available that assess the subchronic and chronic exposure to MMT regardless of the route of exposure, *i.e.* dermal, inhalation, or oral. Nonetheless, ORD's Office of Health and Environmental Assessment has initiated an effort to fully examine the existing oral toxicity data of MMT in the hope of developing a RfD for MMT. This action was precipitated by preliminary findings from ORD's Environmental Research Laboratory (Athens, Georgia) which has suggested that pure MMT can exist as such in various aqueous environments for an appreciable period of time.

REFERENCES

Aschner, M. and J.L. Aschner. 1990. Manganese transport across the blood-brain barrier: Relationship to iron homeostasis. Brain Res. Bull. 24: 857-860.

ATSDR. 1988. The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress. Agency for Toxic Substances and Disease Registry, Atlanta, GA. 30333.

Barnes, D.G. and M. Dourson. 1988. Reference dose (RfD): Description and use in health risk assessments. Reg. Tox. Pharm. 8:471-486.

Cahill, D.F., M.S. Bercegeay, R.C. Haggerty, J.E. Gerding, and L.E. Gray, 1980. Age-related retention and distribution of injested Mn_3O_4 in the rat. Toxicol. Appl. Pharmacol. 53: 83-91.

Chandra, S. V., G. S. Shukla, R.S. Strivastava, H. Singh, and V.P. Gupta, 1981. An exploratory study of manganese exposure to welders. Clin. Toxicol. 18: 407-416.

Collipp, P. J., S. Y. Chen, and S. Maitinsky, 1983. Manganese in infant formulas and learning disability. Ann. Nutr. Metab. 27:488-494.

Davis, J. M., and D. J. Svendsgaard, 1987. Lead and child development. Nature 329: 297-301.

Davis, J.M., and D.J. Svendsgaard, 1990. U-shaped dose-response curves: their occurrence and implications for risk assessment. J. Tox. Environ. Health 30: 71-83.

Donaldson, J. 1987. The physiopathologic significance of Mn in the brain: its relation to schizophrenia and neurodegenerative disorders. Neurotoxicology 8: 451-462.

Drown, D. B., S. G. Oberg and R. P. Sharma. 1986. Pulmonary clearance of soluble and insoluble forms of manganese. J. Tox. Environ. Health 17: 201-212.

Ethyl Corporation. 1977. A Medical guide. "Ethyl" MMT. Unpublished report submitted to EPA, Office of Toxic Substances, August 9, 1983. FYI-OTS-0883-0253.

Ethyl Corporation. 1976. Material Safety Data Sheet for MMT. Houston, TX: Ethyl Corporation.

Hakkinen, P. J. and W.M. Haschek. 1982. Pulmonary toxicity of methylcyclopentadienyl manganese tricarbonyl: noncilliated bronchiolar epithelial

(Clara) cell necrosis and alveolar damage in the mouse, rat, and hamster. Toxicol. Appl. Pharmacol. 65: 11-22.

Hinderer, R.K. 1979. Toxicity studies of methylcyclopentadienyl manganese tricarbonyl (MMT). Amer. Ind. Hyg. Assoc. J. 40: 164-167.

Hurley, L.S. and Keen, C. L. 1987. Manganese. In W. Mertz, ed., Trace Elements in Human and Animal Nutrition, Vol. 1. Academic Press, Orlando, Fla. Pp. 185-223.

Iregren, A. 1990. Psychological test performance in foundary workers exposed to low levels of manganese. Neurotox. Teratol. 12: in press. (Nov.-Dec. issue)

Jarabek, A., M. Menache, J. Overton, M. Dourson and F. Miller. 1989. Inhalation Reference Dose (RfD): An application of interspecies dosimetry modeling for risk assessment of insoluble particles. Health Physics. 57 (Suppk 1) 117-183.

Lauwerys, R., H. Roels, P. Genet, G. Toussaint, A. Bouckaert, and S. De Cooman. 1985. Fertility of male workers exposed to mercury vapor or to manganese dust: a questionnaire study. Am. J. Indust. Med. 7: 171-176.

Lloyd-Davies, T.A. 1946. Manganese pneumonitis. Br. J. Ind. Med. 3: 111-135.

Mena, I., K. Horiuchi, K. Burke and G.C. Cotzias. 1969. Chronic manganese poisoning: Individual susceptibility and absorption of iron. Neurology 19: 1000-1006.

NAS. 1973. Medical and Biologic Effects of Environmental Pollutants. Committee on Biologic Effects of Atmospheric Pollutants. Division of Medical Sciences. National Research Council, National Academy of Sciences, Washington, D.C.

National Research Council. 1989. Recommended Dietary Allowances, 10th edition, National Academy Press, Washington, D.C.

Newland M. C., C. Cox, R. Hamada, G. Oberdorster and B. Weiss. 1987. The clearance of manganese chloride in the primate. Fund. Appl. Tox. 9: 314-328.

Nishiyama, K., Y. Suzuki, N. Fujii, H. Yano, T. Miyai and K. Ohmishi. 1975. Effect of long-term inhalation of manganese dusts. II. Continuous observation of the respiratory organs of monkeys and mice. Jpn. J. Hyg. 30 (1): 117.

Nogawa, K., E. Kobayashi, M. Sakamoto, N. Fukushima, A. Ishizaki, N. Makino, S. Kagamimor, Y. Hiramaru, S. Kawano, T. Kato and K. Kanekawa, Shozo. 1973. Studies of the effects on the respiratory organs of air pollution consisting of dusts composed mainly of manganese. (First Report). Effects on respiratory organs of junior high school students. Japan J. Public Health, 20: 315-326 (Translated from Japanese.)

Pennington, J.A.T., B. E. Young and D. B. Wilson. 1989. Nutritional elements in U.S. diets: results from the Total Diet Study, 1982-86. J. Am. Diet Assoc. 89:659-664.

Perl, D. P. and Good, P.F. 1987. Uptake of aluminum into central nervous systems along nasal-olfactory pathways. Lancet, May 2, 1978.

Roels, H., R. Lauwerys, J-P. Buchet, P. Genet, M.J. Sarhan, I. Hanotiau, M. de Fays, A. Bernard and D. Stanescu. 1987. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am. J. Indust. Med. 11: 307-337.

Schroeder, H. A., J. J. Balassa and I. H. Tipton. 1966. Essential trace metals in man: manganese, a study in homeostasis. J. Chron. Dis. 19:545-571.

Shiotsuka, R.N. 1984. Inhalation toxicity of manganese dioxide and a magnesium oxide-manganese dioxide mixture. GRAI. 85: 34.

Suzuki, Y. , N. Fujii, H. Yano, T. Ohkita, A. Ichikawa and K. Nishiyama. 1978. Effects of the inhalation of manganese dioxide dust on monkey lungs. Tokushima J. Exp. Med. 25: 119-125.

Ter Haar, G.L., M.E. Griffing, M. Brandt, D.G. Oberding, M. Kapron, M. 1975. Methylcyclopentadienyl manganese tricarbonyl as an antiknock: composition and fate of manganese exhaust products. J. Air Pollut. Control Assoc. 25: 858-860

Underwood, E.J. 1981. The incidence of trace element deficiency diseases. Phil. Tran. R. Soc. Lond. B 294:3-8.

U.S. Environmental Protection Agency. 1984. Health Assessment Document for Manganese. Environmental Criteria and Assessment Office, Cincinnati, OH, EPA-600/8-83/013F.

U.S. Environmental Protection Agency. 1986. Air Quality Criteria for Lead. ECAO/OHEA/ORD, U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA-600/8-83/028a-dF.

U.S. Environmental Protection Agency. 1990a. Interim methods for development of inhalation reference doses. ECAO/OHEA/ORD, U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA/600/8-88/066F.

U.S. Environmental Protection Agency. 1990b. Air Quality Criteria for Lead: Supplement to the 1986 Addendum. ECAO/OHEA/ORD, U.S. Environmental Protection Agency, RTP, NC. EPA-600/8-89/049F.

U.S. Environmental Protection Agency. 1990c. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

Wieczorek, H. and G. Oberdorster, 1989. Kinetics of inhaled $^{54}MnCl_2$ aerosols: Influence of inhaled concentration. Polish J. Occup. Med. 2: 248-260.

WHO. 1973, Trace Elements in Human Nutrition: Manganese. Report of a WHO Expert Committee, Technical Report Service, 532. World Health Organization, Geneva, Switzerland. Pp. 34-36.

WHO, 1987. Manganese. In: Air Quality Guidelines for Europe. WHO Regional Publications, European Series No. 23., Denmark, pp. 262-271.

Attachment 2

EMISSIONS AND MANGANESE (Mn) LEVELS IN MICROENVIRONMENTS

A. Emissions

In its fuel additive waiver application of May 9, 1990, Ethyl Corporation recommended a manganese concentration of 1/32 gram of Mn per gallon of unleaded gasoline. The application contained extensive regulated gaseous emission data concerning hydrocarbons (HC), carbon monoxide (CO), and oxides of nitrogen (NOx).

Based on ORD's Atmospheric Research and Exposure Assessment Laboratory's (AREAL) review of Ethyl's vehicle emission studies, it appears that the there are significant uncertainties associated with the data on manganese particulate emissions, emitted in the form of Mn_3O_4. In its studies, Ethyl measured airborne particulate matter for three model groups of vehicles (a total of 9 test vehicles) at only one test point of 75,000 miles. These data were measured in accordance with the Federal Test Procedure (FTP). (Later, on August 23, 1990, Ethyl submitted limited non-FTP test data that will be commented upon below.) Although the particulate sampling procedure used was the EPA-recommended method, which is primarily used for diesel particulate sampling studies, the experimental details of the sampling procedure exployed were not disclosed. For example, no information was provided on the configuration of the test apparatus, the flow rate through the dilution tunnel, the flow rate through the filter medium, the type of filter medium used, the filter loading in terms of mass per unit area (i.e., $\mu g/cm^2$), and the temperatures and pressures used. Also, it was uncertain whether other FTP particulate tests has been run prior to the only one reported at 75,000 miles for the test vehicles. This single reported FTP particulate test was at 75,000 miles, with Ethyl indicating an average FTP manganese emission rate of 5 µg/mile, i.e., only 0.4 percent of the manganese was exhausted from the tailpipe. The other 99.6 percent of combusted manganese was unaccounted for and unexplained by Ethyl.

There are insufficient data presented (i.e., only one particle data point in 75,000 miles) to justify Ethyl's conclusion that this Mn emission rate of 5 µg/mile is representative of 1/32 g Mn/gal-fueled vehicles. In Ethyl's most recent submission (August 23, 1990), it provided steady state particulate emission data (at speeds of 25, 45, and 60 mph) that indicated particulate emissions of up to 60 µg/mile, i.e., 7 percent of the added Mn being exhausted from the tailpipe. Ethyl states that "in order to be conservative, manganese emissions that result from use of the additive could range up to 30 percent of the manganese in the additive" (p. 22-23 of Ethyl's

"Comments in support of the waiver application for the HiTEC 3000 Performance Additive, July 23, 1990). This means that the average Mn FTP emission rate could be as high as 375 μg/mile (for a 20 mile/gallon vehicle), or 30 percent of the added manganese being exhausted from the tailpipe. This still leaves 70 percent of the manganese combusted unaccounted for.

Ethyl's explanation to account for the 'missing' (i.e., the non-tailpipe-emitted) manganese is as follows:

> "While some have suggested that Ethyl should perform a material balance to determine how much of the manganese in the Additive is emitted from the tailpipe, a material balance in this case would be difficult to perform and fraught with uncertainty. For example, the goal of this analysis would be to account for all of an extremely small amount of material (only about 90 grams if all the manganese in the Additive remained in the test vehicles) from at least 10,000 to 15,000 square centimeters of surface area. There is no standardized method for conducting such an analysis of materials from an automobile. It would require all of the parts of the automobile that might retain manganese from the Additive (e.g., the combustion chambers, pistons, spark plugs, manifolds, the catalyst, the exhaust pipe(s), and the engine oil and filter) to be removed from the car, their coatings extracted and dissolved in acid, and the remaining solution analyzed for the presence of manganese. To gain access to these surface areas, various components of the automobile would have to be disassembled either directly or by cutting them up. This aspect of the analysis alone would generate substantial uncertainties regarding ultimate results -- e.g., how much of the manganese would be removed from these components simply as a result of the physical removal process? Given the complexity and uncertainties of conducting a material balance, and that emissions (not a material balance) is ultimately the relevant issue to this proceeding, Ethyl has chosen to be conservative by relying on information from the testing of older vehicles without catalytic converters, and assuming that 30 percent of the manganese would be emitted from new vehicles using the Additive."

This explanation begs the question. It is not clear why a method(s) could not be devised to account for the manganese in the engine and exhaust system; internal photographs coupled with even approximate analyses would be helpful.

ORD understands that current studies underway at EPA-Ann Arbor indicate that MMT use at 1/32 g μg/gal appears to result in increased levels of total particulate matter that cannot be accounted for on the basis of increased manganese emissions alone.

Other Uncertainties and Comments Regarding Emissions

1) Data have not been provided that indicate the size distribution of the manganese-containing particles that are being emitted from the tailpipe. It is uncertain whether the manganese particles affect the other (non-manganese) particulate being emitted.

2) If manganese particle emissions are similar in property to those of lead, the percentage of manganese exhausted will vary with the vehicle's operating condition and will increase when the vehicle accelerates from a stop or low speed cruise mode (20 mph) to a much higher speed (60 mph). This occurs because particles build up in the exhaust system during steady-state driving and are subsequently released during high-load accelerations. Perhaps a simple test procedure simulating a low speed cruise to a high-load acceleration could be devised and tested at EPA-Ann Arbor to see if the Mn particle emissions vary significantly with driving mode. If they do, then personnel working in toll booths, parking garages, or street canyons will certainly receive a significantly greater exposure to manganese exhaust than office workers (as considered by ORD in its modeling scenarios, Attachment 3).

3) It is uncertain whether MMT will be used in oxygenated fuel blends and, if so, whether it will have a positive or negative impact on formaldehyde emissions.

4) It is unlikely that MMT would comprise any significant fraction of evaporative or refueling vapor emissions, because of its low vapor pressure (0.0019 psi at 77°F) compared to other gasoline components. For example, the major components of a typical refueling vapor include the paraffins isobutane, butane, isopentane, and pentane, all of which have vapor pressures orders of magnitude higher. These four paraffins typically comprise 70 percent by weight of the total refueling vapor. ORD notes that Ethyl's reported evaporative emission tests on 8 vehicles of its test fleet indicated MMT had no effect on evaporative emissions.

B. Manganese Levels in Microenvironments

Tables 1 and 2 detail calculated ambient manganese concentrations in terms of $\mu g/m^3$ from mobile sources in seven microenvironment scenarios. The tabulated concentrations do not take into account the estimated Mn background concentration of 0.04 $\mu g/m^3$. The tables depict scenarios for vehicles with a 20 and 25 mile per gallon fuel economy. The seven microenvironment scenarios include a residential garage, a parking garage, a roadway tunnel, a street canyon, an on-an-expressway (receptor = vehicle occupant) scenario, and a beside-an-expressway scenario for both short term (less than 1 hour) and annual average exposures. Five different manganese tailpipe emission rates (in g/mile) were chosen, 100 percent (representing 100 percent of Mn into engine = Mn exhausted out the tailpipe), 60 percent, 40 percent, 30 percent, 20 percent, 10 percent, and 0.4 percent. The 0.4

percent tailpipe Mn emission rate represents Ethyl's observed Mn particulate emission rate, while the 30 percent Mn emission rate represents Ethyl's upper estimate of Mn particulate emissions (see Attachment 3-23, Appendix 3, Volume 2 of Ethyl's waiver application).

The microenvironment scenarios and factors used are taken from a paper by Ingalls and Garbe (1982). The concentrations calculated in the scenarios have not been validated by field monitoring studies. A constant fuel economy of 20 mpg was assumed for microenvironment scenarios #3, 5, 6 and 7; 10 mpg was assumed for scenario #4; and idle fuel consumption rates were assumed for the residential and parking garage scenarios.

References

Ingalls, M.N., and Garbe, R.J., (1982): Ambient pollutant concentrations from mobile sources in microscale situations. SAE Technical Paper Series 820787. Presented at Passenger Car Meeting, Troy, MI, June 7-10, 1982. 15 pp.

Table 2- 1: Calculated Manganese Pollutant Concentrations in µg/m3* of Mn for **20** miles/gallon Vehicle Fuel Economy with 1/32 gram/gallon Mn Fuel Additive (MMT)

Micro-environment Scenario (20 mpg in scenarios #3,5,6,7)	Tailpipe-out Mn Emission Rates: (100% Exhausted) 1563 µg/mile	(60% E.) 938 µg/mile	(40% E.) 625µg/mile	(30% E.) 469 µg/mile	(20% E.) 313µg/mile	(10% E.) 156 µg/mile	(0.4% E.) 6 µg/mile
1. Residential Garage[1]							
Typical (30 sec run time)	2.50	1.50	1.00	0.75	0.50	0.25	0.010
Severe (5 minute run time)	21.16	12.70	8.46	6.35	4.23	2.12	0.085
2. Parking Garage[1]							
Typical	1.23	0.74	0.49	0.37	0.25	0.12	0.005
Severe	17.60	10.56	7.04	5.28	3.52	1.76	0.070
3. Roadway Tunnel							
Typical	1.76	1.05	0.70	0.53	0.35	0.18	0.007
Severe	4.46	2.68	1.78	1.34	0.89	0.45	0.018
4. Street Canyon (sidewalk receptor)[2]							
Typical a) 800 vehicles/hr	0.14	0.08	0.06	0.04	0.03	0.014	0.0006
b) 1600 vehicles/hr	0.26	0.16	0.10	0.08	0.05	0.026	0.0010
Severe a) 1200 vehicles/hr	0.44	0.26	0.18	0.13	0.09	0.044	0.0018
b) 2400 vehicles/hr	0.88	0.52	0.35	0.26	0.18	0.088	0.0036
5. On Expressway							
Typical	0.19	0.11	0.08	0.06	0.04	0.019	0.0008
Severe	0.79	0.47	0.32	0.24	0.16	0.079	0.0032

Table 2-1-Continued

Micro-environment Scenario (20 mpg in scenarios #3,5,6,7)	Tailpipe-out Mn Emission Rates: (100% Exhausted) 1563 µg/mile	(60% E.) 938 µg/mile	(40% E.) 625µg/mile	(30% E.) 469 µg/mile	(20% E.) 313µg/mile	(10% E.) 156 µg/mile	(0.4% E.) 6 µg/mile
6. Beside Expressway (Severe-Short term)							
1 meter	0.62	0.37	0.25	0.19	0.12	0.062	0.0025
10 meters	0.52	0.31	0.21	0.16	0.10	0.052	0.0021
100 meters	0.16	0.10	0.06	0.05	0.03	0.016	0.0006
1000 meters	0.02	0.01	0.008	0.006	0.004	0.002	0.0001
7. Beside Expressway (Annual average)							
1 meter	0.095	0.057	0.038	0.029	0.019	0.0095	0.00038
10 meters	0.075	0.045	0.030	0.023	0.015	0.0075	0.00030
100 meters	0.022	0.013	0.009	0.007	0.004	0.0022	0.00009
1000 meters	0.003	0.002	0.001	0.001	0.0006	0.0003	0.00001

* Adapted from SAE Paper No. 820787, "Ambient Pollutant Concentrations from Mobile Sources in Microscale Situations" by Melvin N. Ingalls and Robert J. Garbe, June 1982. Assumes no Mn background concentration.

1. Based on actual 5-minute idle fuel consumption tests indicating an idle fuel consumption rate = 0.0101 gal/minute.
2. Assumes a 10 mile/gallon vehicle fuel economy for street canyon scenarios.

Table 2-2: Calculated Manganese Pollutant Concentrations in µg/m3* of Mn for **25** miles/gallon Vehicle Fuel Economy with 1/32 gram/gallon Mn Fuel Additive (MMT).

Micro-environment Scenario (25 mpg in scenarios #3,5,6,7)	Tailpipe-out Mn Emission Rates: (100% Exhausted) 1250µg/mile	(60% E.) 750µg/mile	(40% E.) 500µg/mile	(30% E.) 375µg/mile	(20% E.) 250µg/lime	(10% E.) 125µg/mile	(0.4% E.) 5µg/mile
1. Residential Garage[1]							
Typical (30 sec run time)	2.00	1.20	0.80	0.60	0.40	0.20	0.008
Severe (5 minute run time)	16.96	10.18	6.78	5.09	5.09	1.70	0.068
2. Parking Garage[1]							
Typical	1.00	0.60	0.40	0.30	0.20	0.10	0.004
Severe	14.10	8.46	5.64	4.23	2.82	1.41	0.056
3. Roadway Tunnel							
Typical	1.40	0.84	0.56	0.42	0.28	0.14	0.006
Severe	3.57	2.14	1.43	1.07	0.71	0.36	0.014
4. Street Canyon (sidewalk receptor)[2]							
Typical a) 800 vehicles/hr	0.10	0.06	0.04	0.03	0.02	0.0010	0.0004
b) 1600 vehicles/hr	0.20	0.12	0.08	0.06	0.04	0.0020	0.0010
Severe a) 1200 vehicles/hr	0.36	0.22	0.14	0.11	0.07	0.0036	0.0014
b) 2400 vehicles/hr	0.70	0.42	0.28	0.21	0.14	0.0070	0.0028
5. On Expressway							
Typical	0.16	0.10	0.06	0.05	0.03	0.015	0.0006
Severe	0.63	0.38	0.25	0.19	0.13	0.063	0.0025

Table 2-2-Continued

Micro-environment Scenario (25 mpg in scenarios #3,5,6,7)	Tailpipe-out Mn Emission Rates: (100% Exhausted) 1250 µg/mile	(60% E.) 750µg/mile	(40% E.) 500 µg/mile	(30% E.) 375 µg/mile	(20% E.) 250µg/mile	(10% E.) 125 µg/mile	(0.4% E.) 5 µg/mile
6. Beside Expressway (Severe-Short term)							
1 meter	0.50	0.30	0.20	0.15	0.10	0.050	0.0020
10 meters	0.42	0.25	0.17	0.13	0.08	0.042	0.0017
100 meters	0.13	0.08	0.05	0.04	0.03	0.013	0.0005
1000 meters	0.02	0.012	0.008	0.006	0.004	0.002	0.0007
7. Beside Expressway (Annual average)							
1 meter	0.076	0.046	0.030	0.023	0.015	0.0076	0.00031
10 meters	0.060	0.036	0.024	0.018	0.012	0.0060	0.00024
100 meters	0.018	0.011	0.007	0.005	0.004	0.0018	0.00007
1000 meters	0.002	0.0012	0.0008	0.0006	0.0004	0.0002	0.00001

* Adapted from SAE Paper No. 820787, "Ambient Pollutant Concentrations from Mobile Sources in Microscale Situations" by Melvin N. Ingalls and Robert J. Garbe, June 1982. Assumes no Mn background concentration.

1. Based on actual 5-minute idle fuel consumption tests indicating an idle fuel consumption rate = 0.008 gal/minute.
2. Assumes a 12.5 mile/gallon vehicle fuel economy for street canyon scenarios.

Attachment 3

ESTIMATES OF DAILY MANGANESE (Mn) EXPOSURE

This attachment provides modeled estimates, performed by ORD's Atmospheric Research and Exposure Assessment Laboratory (AREAL), of the average Mn inhalation exposures to humans due to use of MMT as an additive in unleaded gasoline.

Outline of the modeling rationale

The model construct is based on the structure and assumptions of the Simulation of Human Activity and Pollutant Exposure (SHAPE) model (Ott et al., 1988). The model computes the integrated daily exposures of persons using the concept of microenvironments. A microenvironment is a location, such as a home, office, or automobile, that a person routinely visits during the natural course of activities in a day. The total inert pollutant concentration in each micro-environment is derived by adding the fraction contributed by sources of the pollutant within the microenvironment to the fraction contributed by ambient background.

The two primary component parts of this model construct are: (1) estimated microenvironmental concentration values and, (2) assumed human activity patterns. ORD decided to estimate the average manganese exposure for a typical office worker. (More severe but less common exposure scenarios could occur, such as those in various occupational settings, e.g., toll takers, parking attendants, and highway construction workers.) In order develop the estimate for the office worker, modeled estimates of concentrations for each microenvironment were derived using an activity pattern defined from summary statistics in available time studies of human activities. In order to estimate the possible distribution of exposures over the diverse activity schedules of an urban population, it was assumed that the manganese exposure distribution from mobile emissions would be similar to that of carbon monoxide.

The manganese exposure distribution estimate has not been validated. Because of the large uncertainties in the concentration estimates for the various microenvironments and the many assumptions made in developing the estimated manganese exposure, the estimate should be considered a screening estimate for the purpose of identifying whether more refined analyses are warranted.

Background

There are several ways to develop exposure estimates. One approach ("the direct method") is to measure exposure directly through the use of personal monitors that are carried by individuals during their normal daily activities. A major concern in such studies is the development of statistically representative samples of individuals from which to extrapolate the results to estimate the general population's exposures. Also, the pollutant or surrogate tracer of the pollutant must exist and be measurable. Such information does not exist for an Mn inhalation exposure assessment.

Another approach (the "indirect method") is to estimate the integrated exposure by estimating the concentration levels in relevant microenvironments and combining these estimates with either real or simulated human activity pattern data. Typically, this involves defining microenvironments within which the individuals are exposed. A microenvironment is defined here as a three-dimensional space where the pollutant level can be specified as a function of time, such as within an automobile on a major expressway or a downtown business office.

The most accurate application of the indirect method requires measurements of pollutant concentrations near roadways, inside homes, offices, motor vehicles, etc. This is not possible for assessment of an unmeasured compound, unless one can use tracer material that disperses in a manner similar to the proposed material. There are no suitable tracer studies that would be sufficient for a MMT assessment. Thus, we must estimate the Mn concentration levels.

Manganese Concentration Levels

For a first analysis, ORD used a scheme, developed by Ingalls and Garbe (1982), to estimate the concentration levels within the various microenvironments contained in Table 2-1 of Attachment 2. The scheme requires estimates of the emission rate of the pollutant. A major modeling uncertainty is that the estimates ignore the complicating factors of time variation in emission rates and time variation in the physical processes affecting the dispersion and transport of Mn. Thus, in themselves, the estimates do not provide a clear indication of the possible variation in concentration levels. (The next step in the analysis will try to capture some of the variability due to this uncertainty.)

ORD estimated the current annual average ambient background Mn concentration to be 0.04 $\mu g/m^3$. The basis for this estimate was observed 24-hour average manganese concentrations from 102 sites across the United States for four years: 1984, 1985, 1986 and 1987. The computed annual average manganese concentrations for these years were: 0.042, 0.041, 0.039 and 0.044 $\mu g/m^3$, respectively.

ORD then estimated the incremental increase in the ambient average background Mn concentration due to the use of MMT in unleaded gasoline, which is 0.05P, where P is the fraction of the total manganese in the fuel that is assumed to be present in the vehicular exhaust. This estimate was developed by assuming a ratio of ambient concentration level (in $\mu g/m^3$) to emission factor (in g/m) of 30:1. Applying this ratio to an emission factor of 0.0016 grams of manganese per mile (equal to 0.03125 gr/gal x 1 gal/20 miles, i.e., assuming 100 percent emissions), yields an ambient average concentration of manganese of 0.05 $\mu g/m^3$.

Several options are available to select a hypothetical subpopulation for the purposes of exposure assessment. In keeping with EPA policy to exercise conservative judgments when actual data are not available, the two key options would be children in urban environments and a class of adults who would be expected to receive relatively high exposure. For children, it was assumed that they would receive inhalation exposures indoors (home and school) or outdoors at play away from urban streets. This would likely result in an exposure lower than adults in an "office worker" class, making the latter the worse case scenario. (Children are likely to be at risk for higher oral exposure than adults and, therefore, are considered as part of the oral exposure assessment.)

Table 3-1 below lists the estimated manganese concentrations for select micro-environments that would result from 100 percent emissions. The micro-environments were chosen in anticipation of those needed for development of an exposure assessment for an office worker who has a home garage, commutes to work in a downtown office, and parks the car in a parking garage relatively near to the office.

In Table 3-1, for microenvironments without Mn sources present, i.e., homes and business offices, the assumed concentration was the background level. Background levels were estimated as the summation of the current ambient level plus the increment due to mobile emissions of manganese. In microenvironments with Mn sources present, the concentration levels were estimated as the summation of that due to sources within the microenvironment plus that due to ambient background. The geometric mean of the "typical" and "severe" concentration estimates was used to characterize the concentration due to sources within the microenvironment. (From Tables 2-1 and 2-2, Attachment 2, the geometric mean was derived by taking the square root of the product of the values for the "typical" and "severe" situations.) For this analysis, the concentration values were based on the results obtained assuming 20 miles per gallon fuel consumption. The addition due to ambient background was assumed to be the same as that estimated for the home and business office microenvironments.

Table 3-1. Manganese (Mn) Concentrations for Select Microenvironments in $\mu g/m^3$ (a)

Microenvironment	Ambient background	Increment to background	Increment from sources	Total
Home	0.04	0.05	0.00	0.09
Home garage	0.04	0.05	7.27	7.36
Expressway	0.04	0.05	0.39	0.48
Urban streets (b)	0.04	0.05	0.48	0.57
Parking garage	0.04	0.05	4.65	4.74
Walking downtown (c)	0.04	0.05	0.57	0.66
Business office	0.04	0.05	0.00	0.09

(a) It is assumed that (1) 100 percent of the Mn is emitted; (2) the 'modeled' emission rates are the geometric means of the "typical" and "severe" emisssion rates, and (3) fuel economy is 20 MPG except in: garage scenarios where idle emission rates are assumed, and street canyons where 10 MPG is assumed;
(b) "Street Canyon" scenarios;
(c) "Beside Expressway" scenarios.

Human Activity Patterns

Given the time provided for this review, ORD could not develop or obtain data regarding human activities tailored to the specific needs of this analysis. Ideally we would have in computer compatible form, daily activity patterns for a sufficient number of 'individuals' to characterize the activities and lifestyles of the population of the United States. Although computer data files of human activities exist for several studies conducted in the United States, it was not feasible to acquire these for use in this analysis. Therefore, two available studies (Ott, 1988 and Winer et al., 1989), whose conclusions were in agreement, were used to develop the activity schedule presented in Table 3-2 for a hypothetical office worker who commutes to an office located in metropolitan city.

The activity schedule does not necessarily use average durations. As is stressed in the two studies themselves, there are significant limitations in using average durations to assess human exposures. To illustrate, consider the characterization of commute time to and from work. It is generally agreed that as

city size increases, the commute increases but only slightly. Of more concern is whether use of the average trip duration is useful. Even though the average one-way commute is roughly 20 to 25 minutes, one third of those commuting have only 10 minute trips, while 3.8 percent of those surveyed have trips of 60 minutes or more. Those having long commute times represent a small, but not negligible, segment of the population. Such variations are quite typical of all the activities engaged in by humans.

Table 3-2. Activity Schedule for Hypothetical Office Worker

Activity	Duration (minutes)
Home (asleep)	480
Home (active)	60
Home Garage	3
Suburban Drive	40
Urban Drive	10
Parking Garage	4
Walk to Office	2
Office	540
Walk to Car	2
Parking Garage	4
Urban Drive	10
Suburban Drive	40
Home Garage	2
Home (active)	243

Manganese Exposure Estimates

Using the concentrations listed in Table 3-1 and the durations listed in Table 3-2, the time-weighted 24-hour concentrations for the hypothetical office worker were calculated for various Mn emission levels. The background increment (due to mobile source emissions) and the microenvironmental concentrations (due to sources emitting within the microenvironments) were linear functions of the percent of Mn assumed to be emitted. The 24-hour accumulated manganese dose was estimated by multiplying the 24-hour concentration by the total amount of air breathed, which is assumed to be 20 μg/day (a standard EPA assumption). The resulting 24-hour Mn concentrations and doses are listed in Table 3-3.

Table 3-3. Estimated 24-hour Mn Concentrations and Inhaled Doses for Hypothetical Office Worker

Percent of manganese emitted	24-hour Concentration ($\mu g/m^3$)	24-hour inhalation dose (μg)
0.4	0.04	0.8
10	0.05	1.1
20	0.07	1.3
30	0.08	1.6
40	0.09	1.8
60	0.12	2.4
100	0.17	3.4

The Mn exposure estimates do not change drastically if the "typical" or "severe" concentration values are used. For example, the total 24-hour dose, assuming 100 percent of the Mn is emitted is 2.4 μg using "typical" concentration values and 6.0 μg using 'severe' concentration values. Considering the uncertainties in the concentration estimates, the differences between 2.4 μg (typical), 3.4 μg (modeled) and 6.0 μg (severe) are not significant.

Interpretation of manganese exposure estimates

ORD then interpreted the results in light of a carbon monoxide (CO) exposure study in Washington, D.C. during November, 1982 to February, 1983. Results from the study are reported in Mage et al. (1989). The activity schedule for a typical office worker was used to estimate an average CO exposure.

Table 3-4 presents CO concentration levels which can be used to estimate CO concentration levels for the microenvironments listed in Table 3-1. The "average" CO concentration values were corrected for background effects. Also presented in Table 3-4 are frequency distribution data for 8-hour CO concentration values.

Table 3-4. Summary of CO Exposure Data from Washington, D.C. Field Study. Part A lists average CO concentrations for select microenvironments corrected for background sources from Mage et al. (1989), Table 4. Part B was extracted from Mage et al. (1989) Figure 1, which depicted the cumulative frequency distribution of 8-hour CO concentration values.

	Part A		Part B	
Microenvironment	Ave. Conc.	S.D.	Percentile (%)	Concentration
Home (1)	0.5	1.61	15	0.6
All automobile			25	1.0
microenvironment (2)	3.9	6.42	50	2.0
			75	3.4
Walking downtown (3)	3.1	9.71	90	5.5
Business office (4)	0.8	2.83	99.4	19.0

S.D. Standard deviation
(1) Mage et al. (1989) 'Sleeping'
(2) Home garage, expressway, urban streets, parking garage
(3) Mage et al. (1989) 'High Exposure'
(4) Mage et al. (1989) 'Office, without smokers'

An estimate of the 24-hour CO exposure of 1.9 ppm is derived by considering the average CO concentrations listed in Table 3-4, and the durations listed in Table 3-2. The background CO concentration was assumed to be 1 ppm. The estimated esposure of 1.9 ppm can be compared to the observed average 8-hour CO exposure listed in Table 3-4 of 2 ppm. It would appear that use of average concentrations and average activity durations can provide order of magnitude estimates of average exposures. But as indicated in Table 3-4, the average exposure says little regarding the maximum exposures.

One important conclusion to be drawn from Table 3-4 is the large variation in CO concentration values as indicated by standard deviations as much as 3 times larger than the average values. This is reflected in the cumulative frequency distribution having values 5 times greater than the average value in 2 percent of the 8-hour average exposure measurements. Some of the variation seen in the CO concentration values likely results from variation in vehicle operating efficiency; but much of the variation reflects variations in activity schedules, occupations and the dispersive states within the microenvironments visited during the course of the day.

Extrapolation to population exposure distribution

ORD then estimated the urban population exposures to Mn, by using an analogy between manganese and CO. ORD's hypothesis is that since CO emissions are dominated by mobile sources, variations in CO exposures will be similar to those of Mn.

The CO exposures results presented in Table 3-4 were obtained using portable CO monitoring instruments carried by non-institutionalized, non-smoking residents, aged 18 to 70. Another source of CO emissions is cigarette smoke. Since the sampled population was non-smoking, ORD assumed that the observed CO exposures were only incidentally affected by emissions other than that from mobile sources. The transportation related CO emissions are strongly dependent on engine operating efficiency, which is a function of vehicle speed, ambient temperature, altitude, and other variables. The Mn emissions resulting from MMT additives have been reported to ORD as being primarily dependent on fuel consumption rate. There are other obvious differences between the two pollutants as CO is a gas and the Mn emissions from MMT are fine mode particles having a mass median diameter of 0.2 to 0.4 μm.

ORD then implemented the extrapolation by assuming that the Mn exposures listed in Table 3-3 were estimates of the average exposure for the urban population. This was assumed because the estimated CO exposure, using the hypothetical activity schedule, resulted in a value similar to that observed on average in the CO exposure study. The Mn exposure values for other percentiles in the exposure distribution were obtained by multiplying the average Mn exposure, resulting from mobile source emissions, by the ratio of the CO exposure, at the percentile in question, divided by the observed average CO exposure.

For example, the 99.4 percentile in the CO distribution was 19.0/2.0 = 9.5 times greater than the observed average CO exposure. For 100 percent emissions of Mn, the 24-hour dose is 3.4 μg, as shown on Table 3-3. Of this dose, 2.62 μg resulted from mobile emissions, and 0.8 μg resulted from sources responsible for the current ambient background of 0.04 $\mu g/m^3$. It was assumed that the sources for the current observed levels of Mn were not mobile sources, and, therefore, current ambient Mn concentrations would not be expected to correlate with ambient CO background concentration values. In all cases, the current ambient background was included after the Mn concentration from mobile emissions had been determined for the desired percentile. Therefore, the estimated 99.4 percentile value in the Mn exposure distribution is estimated as (9.5 x 2.62) + 0.8 = 25.7 μg. By an analogous procedure, estimates were obtained for other percentiles and other assumed percentages of Mn emissions. Table 3-5 lists the results obtained.

Table 3-5. Estimates of 24-hour Mn Inhalation Doses (in μg) for Urban Populations for Various Assumed Levels of Mn Emission Fractions

Percent of Mn emitted	Percentile in exposure distribution 85%	75%	50%	25%	10%	0.6%
0.4	0.8	0.8	0.8	0.8	0.8	0.9
10	0.9	0.9	1.1	1.2	1.5	3.3
20	1.0	1.1	1.3	1.7	2.3	5.8
30	1.0	1.2	1.6	2.1	3.0	8.3
40	1.1	1.3	1.8	2.6	3.7	10.7
60	1.3	1.6	2.4	3.5	5.2	15.7
100	1.6	2.1	3.4	5.2	8.1	25.7

Conclusions

Although the extrapolation technique outlined in this section has significant limitations, it was developed to provide a logical procedure for obtaining a screening estimate of the distribution of Mn inhalation exposures that might be experienced by urban populations due to MMT additives in unleaded gasoline. The resulting exposure estimates are viewed as order of magnitude estimates. The decimal place accuracies given in the various tables were provided so that the process could be understood and followed, not because such accuracy was deemed significant.

ORD's use of the CO exposure distribution as a surrogate for the variation to be seen in the Mn mobile source exposures suggests that a sizable segment of the population, say 15 percent or so, would experience Mn concentrations 2 to 5 times greater than the "typical exposure." Assuming the hypothetical office worker's exposure is a reasonable surrogate for the rest of the people in a metropolitan area, then average 24-hour doses of Mn with 30 percent emissions of Mn would be 1.6 μg, and we would expect moderate manganese doses of from 2 to 3 μg, with occasional (1 percent or less) doses of 8 μg.

ORD has assumed that variations in Mn exposure values from mobile sources are similar in nature and magnitude as seen in CO exposure measurements. There are sources of CO emissions other than related to transportation, and these other sources may be contributing to some of the dispersion seen in the cumulative frequency distribution of CO exposure values. Furthermore, 8-hour concentration averages typically have greater dispersion than 24-hour concentration averages. For these reasons, the analysis may have overestimated the possible variations in exposures. However, there are many sources of uncertainty in this analysis. The

procedure should be viewed in the spirit of its designed purpose, i.e., as a screening tool for an order of magnitude estimate.

More refined analyses involving extensive field experiments would be needed to develop a refined characterization of air pathway human exposure estimates resulting from MMT in unleaded gasoline. At present, human exposure modeling is just beginning. Years ago, researchers recognized the importance of having good field measurements of human exposures and started the development of personal exposure measurement devices. Many of the uncertainties alluded to in this discussion would be reduced if there were microenvironment human exposure measurements for comparison with the modeling results.

References

Ingalls, M.N., and Garbe, R.J., (1982): Ambient pollutant concentrations from mobile sources in microscale situations. SAE Technical Paper Series 820787. Presented at Passenger Car Meeting Troy, MI, June 7 -10. 15pp.

Mage, D., Ott, W., and Thomas, J., (1989): Comparison of microenvironmental CO concentrations in two cities for human exposure modeling. Presented at 1989 EPA/A&WMA Symposium on Total Exposure Assessment Methodology, November 27 - 30, 1989, Las Vegas, NV, 18pp.

Ott, W.R. (1988): Human activity patterns: a review of the literature for estimating time spent indoors, outdoors, and in transit. Presented at the Research Planning Conference on Human Activity Patterns, Las Vegas, NV, May 10 - 12, 42 pp.

Ott, W., Thomas, J., Mage, D., Wallace, L. (1988): Validation of the Simulation of Human Activity and Pollutant Exposure (SHAPE) model using paired days from the Denver, Colorado, carbon monoxide field study. Atmospheric Environment, (22):2101-2113.

Winer, A.M., Lurmann, F.W., Coyner, L.A., Colome, S.D., and Poe, M.P. (1989): Characterization of Air Pollutant Exposures in the California South Coast Air Basin: Application of a New Regional Human Exposure (REHEX) Model. Final Report contract Number TSA 106-01-88, South Coast Air Quality Management District/California State University Fullerton Foundation. 274 pp.

Attachment 4

ANALYSIS OF THE EFFECT OF MMT ON HUMAN EXPOSURE THROUGH SOIL INGESTION BY CHILDREN AND ADULTS, AND CONSIDERATION OF Mn UPTAKE BY PLANTS

This attachment contains an analysis of indirect exposure to Mn as a result of the introduction of MMT into unleaded gasoline, prepared by ORD's Office of Health and Environmental Assessment (OHEA).

I. Soil Ingestion

The Office of Air Quality Planning and Standards (OAQPS) has indicated that the average urban air concentration is 0.04 $\mu g/m^3$ Mn. For this analysis, ORD considered values of ambient air Mn concentrations of 0.10 $\mu g/m^3$, 1.0 $\mu g/m^3$, and 10 $\mu g/m^3$. According to data reported by the National Academy of Sciences, which indicated a 0.10 $\mu g/m^3$ in urban air concentration, the Mn concentration in precipitation was approximately 0.012 ppm. Monthly average deposition data ranged from 0 to 54 g/ha month with the 0 values occurring at coastal locations. The arithmetic average of the non-zero values, 33.5 g/ha month, is used in the following calculations:

$$33.5 \text{ (g/ha mo)} \times 1 \text{ ha}/ 10000 \text{ m}^2 = 33.5\text{E-}04 \text{ g/m}^2 \text{ mo}$$
$$= 0.0396 \text{ g/m}^2 \text{ yr}$$
$$= 39.6 \text{ mg/m}^2 \text{ yr}$$

Assuming uniform mixing in the top 10 cm of soil,

100,000 cm^3 in slice 1 x 1 x .1 m
soil bulk density = 1.3 g/cm3
100,000 x 1.3 = 130,000 g = 130 kg
39.6 mg/m2 yr / 130 kg = 0.3 mg/kg yr

Assuming that (1) there is no resuspension of Mn and it is not removed by other mechanisms (e.g., erosion, leaching, plant uptake), and (2) Mn deposition is proportional to atmospheric concentration by the ratio observed in the NAS data, and (3) atmospheric concentrations of Mn increased from 0.1 to 1.0 $\mu g/m^3$, the Mn addition to soil could increase the concentration at a rate of 3 mg/kg yr. In 333 years this would double an assumed (upper estimate) background concentration of 1000 mg/kg and the Mn intake from soil ingestion by children would increase from 0.001 to 0.002 mg/kg day. If the atmospheric concentration were to be increased to 1.5 $\mu g/m^3$, the doubling of soil concentration and ingestion dose rate would occur in 222

years. If the atmospheric concentration were increased to 10 $\mu g/m^3$, the doubling of soil concentration would occur in 33 years.

The Lifetime Average Daily Dose (LADD) of Mn from soil ingestion was estimated using the following assumptions:

- ingestion rate = 200 mg/day (child); 100 mg/day (adult)
- exposure duration = 6 yrs (child); 70 yrs (adult)
- exposure frequency = 365 days/yr
- body weight = 16 kg (child); 70 kg (adult)
- averaging time = 70 yr

Mn levels in soil would have to accumulate to levels exceeding 7 percent before soil ingestion would create a dose exceeding an RfD of 0.1 mg/kg day in adults. For a child scenario, the soil concentration would have to exceed 9 percent. (Although children are a sensitive subgroup, the different assumptions used in the analysis result in a higher percentage than adults.)

At the highest air concentration considered above (10 $\mu g/m^3$), it would take 3000 years to exceed 9 percent Mn in soil. The length of time required to reach a soil level that would exceed the RfD depends upon the air concentration as indicated in the following table:

Air conc ($\mu g/m^3$)	Years to reach 90000 mg/kg
1	30,000
10	3,000
100	300

II. Plant Uptake

Plant uptake of Mn from soil occurs readily in all plants with the greatest concentrations occurring in seeds and new growth. The ability of plants to absorb Mn varies according to species. Concentrations of 780 to 930 ppm are common in tea leaves (1.4 - 3.6 mg/L in liquid tea) and as high as 1300 ppm in lettuce. Plant species and varieties differ widely in their tolerance to excess Mn in soils. Some authors have suggested that Mn deficiency in cereals could be largely overcome by selecting varieties that are more efficient in extracting Mn from the soil. For a wide range of plants, Mn deficiency has been reported when plant tops contained <20 ppm Mn on a dry weight basis; and concentrations of 20--500 ppm have been considered adequate but not toxic.

Average soil concentrations probably range from 500 to 900 mg/kg (NAS/NRC, 1973). The total Mn content of soil is of little biological significance (plant uptake is not proportional to total Mn concentration) since only a small

amount is present in an available form. Mn availability in plants is affected by many interrelated factors including:

- concentrations of other cations and total salts,
- pH,
- cation-exchange capacity,
- drainage,
- organic matter content,
- temperature,
- soil compaction,
- microbial activity, and
- concentrations of total or easily reducible Mn in soil.

Plants absorb Mn primarily in the divalent state (Mn^{2+}). This valance state may be achieved by lowering pH, or reducing aeration by flooding or compaction. In flooded soils, temporary toxic concentrations of divalent Mn can occur at Ph 7; this reduction process is favored by higher soil temperatures. In moderately well drained soils, Mn toxicity is generally found only if the soil pH is less than 5.5. Mn deficiency is most common between pH 6.5 and 8.0. Mn deficiency is most common in small grains and soybeans, but also occurs in other crops including corn, peanut, cotton, sweet potato, sugarbeet, potato, sorghum, and mint.

For crops in general, adequate concentrations of exchangeable Mn range between 0.2 and 3 ppm and concentrations of easily reducible Mn range between 9 and 60 ppm. The presence and concentration of other cations is important; soil with 136 ppm was not toxic to alfalfa because a higher concentration of exchangeable Ca reduced the Mn uptake.

In summary, it is difficult to predict what increase in plant concentrations of Mn would occur as a result of the use of MMT as a fuel additive. The effects on agriculture might be beneficial considering that Mn is added to many soils as fertilizer.

Reference

Medical and Biological Effects of Environmental Pollutants: Manganese. National Academy of Sciences, Washington, D.C. (1973), p. 36.

Attachment 5

EXPOSURE TO MMT FROM ACCIDENTAL RELEASES

Introduction

ORD's Athens (Georgia) Environmental Research Laboratory (ERL-Athens) estimates that if MMT is approved for use in gasoline at about 1/32 grams per gallon, over 1,000,000 gallons of MMT would be required each year for U.S. automobiles, a quantity large enough to warrant consideration of potential risk in accident scenarios. ERL-Athens, therefore, undertook a preliminary screening investigation to determine whether there were any potential health and environmental risks from accidental releases of MMT during its manufacture, handling, transportation, storage, and mixing.

In order to make meaningful exposure assessments, either for humans or key environmental species, the environmental fate of MMT must be understood. If the chemical degrades rapidly to innocuous products, exposure will be very limited; if persistent, MMT will accumulate in the environment and both environmental and human exposure are certain to occur at some level. A search of several chemical fate data bases available at ERL-Athens disclosed very little information on MMT -- one article in the French literature indicating that MMT absorbs to sediments and is stable in sediment systems, and another describing its rapid atmospheric photolytic degradation.

Investigations included both environmental fate "screening" experiments and preliminary exposure assessments for several accidental release scenarios. Since it is known that MMT photolyzes rapidly in sunlight in the atmosphere -- its half-life is approximately 2 minutes -- human and environmental exposure scenarios were focused on the spillage or leakage of pure MMT or MMT mixed with gasoline onto soil or into the subsurface environment from transportation accidents or storage tanks.

Environmental Fate Studies

MMT, like most organic (and metallo-organic) chemicals, can conceivably degrade by several reaction pathways -- hydrolysis, photolysis, reduction, oxidation, and microbial degradation -- and may also physically adsorb and volatilize. Experiments were designed to screen the degradation of MMT so as to detect the degradation pathways that may operate significantly over a short time period. Careful kinetic experiments lasting approximately a week can be extrapolated to much longer periods of time to predict reaction half-lives and chemical persistence. ERL-Athens did not measure physical phenomena -- sorption or volatility -- directly. Sorption to environmental solids does certainly occur and influences the

chemical reactivity and transport of MMT. Although MMT is fairly volatile, volatility was not deemed an important transport process for the subsurface release scenarios considered.

The screening experiments would have detected degradation by any of the natural processes mentioned above. Delayed degradation could occur, and remain undetected in the screening studies by microorganisms especially cultivated and acclimatized to degrade MMT. The experimental matrices were of natural origin and would have included a population of microbes representative of the sediments, aquifer materials, and water collected for the experiments but not acclimatized or previously exposed to MMT. Photolysis of MMT is extremely rapid in air in sunlight; care had to be taken, therefore, to protect the reaction vessels from sunlight or room light when screening for other degradation mechanisms, since it was expected that photolysis in water is also rapid. The efficacy of aquatic photolysis was borne out by a separate experiment.

Fate Experiments

Preliminary stability studies were conducted on MMT in an anaerobic sediment-water system, aerobic aquifer material, and distilled water (pH 6.9). Five milliliters of sediment-water (20 percent sediment, weight/weight), aquifer material-water (50 percent solids) or distilled water was spiked with 50 µl of a stock solution of 1.8×10^{-2} molar MMT in ethanol (EtOH) to give a final concentration of 0.2 millimolar. All samples (except one purposely exposed to sunlight) were wrapped in aluminum foil to eliminate photolysis as a degradation pathway. Samples were extracted (solids were not separated) with 1.0 ml of isooctane at various recorded time intervals. The extracts were analyzed for MMT using a Hewlett-Packard benchtop GC/MS equipped with a DB-1 column operated isothermally at 80°C, with an injector temperature of 200°C. The procedural and analytical experimental error was ±10 percent.

Experimental Results

There was no detectable reaction of MMT within experimental error after 3020 minutes in distilled water in the dark. This corresponds to an estimated minimum half-life of 13 days, assuming the 10 percent experimental error could mask a slow reaction. In the anaerobic sediment-water system, there was no detectable reaction within experimental error after 4110 minutes, giving an estimated minimum half-life of 18 days. There was no detectable reaction of MMT in the aerobic aquifer material after 11,420 minutes, corresponding to an estimated minimum half-life of 52 days. Minimum half-lives calculated from the 10 percent error limit are different for each system because kinetic studies for the three different reaction systems were not started at the same time, and yet had to be stopped early. These estimates should not imply that MMT has a short half-life, but

are a lower limit imposed by the experimental error and short experimental time frame. In fact, MMT is very likely to be stable for several months or longer in each system.

An aqueous solution of MMT in pyrex tubes was exposed to outdoor sunlight (near noon) for 2 hours. No MMT could be detected after two hours of photolysis; GC/MS analysis of the isooctane extract, however, indicated an unknown organic photolysis product that did not contain manganese. In addition, a dark colored precipitate, probably manganese dioxide, was observed.

Estimates for Ingestion Exposure to MMT

Several possible pathways exist for exposure to MMT by ingestion, considering the probable industrial use of MMT. Exposure from a direct spill (or leak from an underground storage tank) of MMT into surface water or onto soil with a shallow water table will result in the highest values for transport of MMT into water used for human consumption. An alternative exposure would result from a spill or leakage of gasoline mixed with MMT, either into surface water or onto soil with a shallow water table.

MMT and MMT-containing Gasoline Spills into Groundwater

In assigning or estimating risk to any exposure scenario, the toxicity response data provide an important step. For MMT, although acute toxicity data exist, there are no established dose limits below which chronic and acute toxicity does not occur. An oral reference dose (RfD) for MMT is being developed by ORD. In lieu of an RfD, a "worst case" situation was considered in which the potable water became saturated with spilled MMT. Therefore, for this screening analysis, ORD chose the lower solubility published, 10 mg/l, as a comparison value.

The significance of any real water threshold limit value is dependent on the error in estimation of the human ingestion threshold limit. Definitive data on the minimum concentration at which health effects are not detectable are needed before risk estimates can be quantified. The above comparison value can be compared to concentrations in groundwater following a gasoline or MMT spill. The concentration of MMT in gasoline is 0.128 g/gallon. (Ethyl has presented the concentration in terms of its manganese component as 1/32 g/gal.) Assuming the groundwater is well mixed with the gasoline, the aqueous concentration of MMT can be calculated.

The gasoline-water partition coefficient of MMT can be assumed to be similar to its octanol-water partition coefficient, Kow = 3,162. MMT is known to be completely miscible in octane, which simulates gasoline. The accuracy of the MMT Kow is

uncertain, however, and MMT solution behavior in octanol may be substantially different from that in octane or gasoline.

This extrapolated Kow value can be applied to estimate the concentration of MMT in groundwater mixed with gasoline:

$$\text{Kow} = \frac{\text{mg/kg MMT in octane}}{\text{mg/l MMT in water}} = 3162\ \text{l/kg}$$

$$3162\ \text{l/kg} = \frac{0.128\ \text{g MMT/gal}/(3785\ \text{ml/gal} \times 0.7\ \text{g octane/ml})}{\text{mg/l MMT in water}}$$

$$\text{MMT in water} = \frac{.0000483}{3162\ \text{l/kg}} = 1.528 \times 10^{-8}\ \text{kg/l} = 0.0153\ \text{mg/l}$$

The accuracy of this estimate of MMT in groundwater depends upon the accuracy of the partition coefficient, which is uncertain, and assumes there is no dilution, leaching (aqueous extraction), or evaporation of the gasoline phase. It is also assumed that no compound which would enhance MMT water solubility or change the partition coefficient (e.g., a detergent, methyl-t-butyl ether, or ethanol) is present in the groundwater. Finally, there is assumed to be no degradation or sorption of MMT as it passes through the unsaturated soil zone. Preliminary degradation experiments indicated no significant degradation of MMT in aquifer systems.

For the case where MMT itself is spilled or leached directly onto the soil, the highest concentration of MMT in water will be at the solubility limit (either 10 mg/l or 70 mg/l, the two values reported in the literature), and the exposure concentrations will depend on dilution. For example, for a spill of 1000 gallons of MMT:

$$1000\ \text{gal.} = 3.785 \times 10^{6}\ \text{ml} = 5.223 \times 10^{9}\ \text{mg MMT}$$

Therefore, 1000 gallons of MMT would pollute 5.223×10^{8} liters, or 1.38×10^{8} gallons of groundwater, at 10 mg/l solubility. Consumption of 1 liter of this water would be about equivalent to ingesting about 10 mg of MMT. Again, this assumes no degradation or sorption of MMT in the unsaturated soil zone, and complete mixing of MMT with the aquifer water, which could be a slow process.

Spills of MMT and Gasoline-Containing MMT into Surface Water

In the case of a spill of gasoline into surface water in direct sunlight, photodegradation would degrade the MMT in a few minutes. If the water is turbid (no light available for photolysis), however, or the spill occurs during darkness, and if the MMT readily adsorbs to suspended sediments, the MMT can be transported to anoxic bottom sediment zones. If there is a spill of "pure" MMT, which is more dense than water, it would settle directly to the bottom, probably avoiding exposure to sunlight, even during the daytime. The preliminary experiments discussed above show MMT to be persistent in anoxic sediment systems. Ingestion of these sediments by aquatic organisms could result in bioaccumulation and indirect human exposure to MMT.

Conclusions

1. MMT is persistent in natural aquatic and soil environments -- e.g., subsurface environments -- in the absence of light; it's half-life is longer than two months, perhaps much longer.

2. Microbial degradation, in addition to abiotic degradation, also appears to be quite slow in natural environments; as with most organic pollutants, however, especially cultivated and acclimatized bacteria could degrade MMT.

3. Experimental fate studies are of a preliminary nature; extended kinetic studies should be performed to allow calculation of accurate rate constants, half-lives, and affects of pH and other environmental variables. Aqueous photodegradation products need to be identified.

4. Spillage or leakage of MMT mixed with gasoline at the concentration of 0.128 gram MMT per gallon onto the soil or into the subsurface environment would not result in accumulation of levels of MMT in groundwater harmful to human health.

5. Pure MMT leaked from a storage vessel directly into the ground could contaminate a substantial volume of groundwater creating a risk for human exposure, since MMT is persistent under these environmental conditions. A safety factor exists, however, because the assumption is made that all MMT is transported through the vadose (unsaturated) zone to the saturated zone. This ignores sorption of MMT on solid phases; some sorption will occur, and the extent of sorption of MMT in such environments needs to be determined. The health impact of such potential exposures cannot be quantified at this time (see Attachment 1, Health Effects.)

6. Pure MMT spilled or leaked into surface water would settle directly to the bottom and partition between water and the sediment. MMT would be persistent in anoxic

bottom zones. This could result in ingestion by aquatic organisms, bioaccumulation in the food chain, and possible exposure to humans as well as to the aquatic biota.

7. Since MMT is a persistent chemical, more formal and accurate environmental and human risk assessments should be conducted.

Attachment 6

EFFECTS OF MMT USAGE ON OZONE FORMATION

This attachment provides ORD's Atmospheric Research and Exposure Assessment Laboratory's (AREAL) comments on Ethyl's arguments and data concerning the effect of adding MMT to gasoline on the production of photochemical smog.

Background

Ozone is produced by a complex series of reactions involving volatile organic compounds (VOCs), oxides of nitrogen (NOx) and sunlight. Removal of VOCs or NOx leads to no ozone formation. It has also long been recognized that the reactivities of VOCs are mostly different. Olefins will produce ozone quickly in the presence of NOx and sunlight followed by aromatics and finally the paraffins. Thus, if the more reactive VOCs are replaced with paraffinic VOCs, less ozone is produced (Finlayson-Pitts and Pitts 1986).

Ethyl's Analysis

Ethyl Corporation's analysis of their test data claims that the use of MMT with gasoline can decrease NOx and CO emissions while increasing VOCs slightly. However, Ethyl indicated that comparisons should not be made with gasolines with and without MMT but with gasolines having equal octane ratings. Therefore, Ethyl Corporation arranged for SAI to use its urban airshed model to determine the effect of MMT on O3 formation from light-duty vehicles (SAI, 1990). The SAI model is a three dimensional grid model with 5 vertical layers making use of pollutant emissions, transport, diffusion, chemical reaction, and removal processes. Two cities were studied with this model: Atlanta and Philadelphia. Howell EEE gasoline was used in these modeling studies. Since MMT raises the octane rating, xylenes had to be added to the Howell gasoline in order to make both gasolines comparable. The increased xylenes causes an increase in reactivity of exhaust, running losses and evaporative losses when compared to the Howell fuel using only MMT. The peak concentration was reduced by about 0.5 percent in both cities when the gasoline contained MMT. SAI calculates that MMT usage is equivalent to removing 170,000 vehicles off the road in Philadelphia and 129,000 vehicles in Atlanta.

Ethyl Corporation also arranged for F. Lurman (Lurman 1990), an atmospheric scientist, to study the reactivity of MMT as an additive to gasoline. Lurman used the Carter reactivity scale to determine the reactivities of light-duty vehicles emissions with xylene-containing gasoline and MMT-containing gasoline. The Carter reactivity method ranks VOCs according to their ozone forming potential in gm of O3 formed per gram of organic added. Therefore, by knowing the

concentrations of the various VOCs emitted by a vehicle, one can calculate the amount of ozone expected to be formed when these VOCs react with NOx in the presence of sunlight.

The Lurman study again showed that the addition of xylenes increases the reactivity of the Howell fuel compared to the same fuel containing only MMT. The MMT-containing fuel showed about a 25 percent reduction in reactivity. Lurman concluded that there should be beneficial effects on ambient ozone levels with the use of MMT.

Three experimental studies were also performed on MMT as an additive. Calspan using 0.55 g/m^3 of manganese showed that visibility is decreased after prolonged irradiation of auto exhaust in a large smog chamber (Calspan 1975). In a similar study, a General Motors research team showed almost no difference in smog formation when exhaust from an MMT/gasoline-powered vehicle was irradiated in a large smog chamber (GM 1990).

The GM group also found that the presence of manganese did not accelerate SO_2 oxidation, although more SO_4^- was found. They concluded that the manganese aerosols served as a sulfate scavenger. In the absence of the Mn, the sulfate was apparently deposited on the walls of the smog chamber.

EPA Studies

Some recent studies were also performed at the EPA/RTP laboratories. EPA scientists found that pure MMT should be photochemically reactive. The lifetime of MMT in the presence of NOx and simulated sunlight ($k_1(NO_2) = 0.3\ min^{-1}$) was found to be approximately 2.5 minutes. CO was the major product, but formaldehyde and dicarbonyls are also expected along with manganese oxide. Pure MMT should produce ozone when photooxidized in the presence of NOx at favorable MMT/NOx ratios.

ORD's Conclusion

ORD concludes, based on our review of the above studies, that MMT in gasoline at the levels proposed the Ethyl Corporation (1/32 gm/gal) should have no adverse effect on air quality in terms of ozone formation. Although MMT is photochemically reactive, its presence in the gas phase would be so low that it would not significantly affect ozone formation. Instead, the presence of MMT as a substitute for xylenes may, in fact, decrease photochemical ozone formation. Visibility appears to be decreased slightly (Calspan study), but this decrease is apparently small since it was not observed until prolonged irradiation of the MMT-containing fuel. Also, the experiments were inconclusive, since a more valid

comparison would require the addition of xylenes (aromatics) to the reference fuel. Aromatics upon photooxidation produce large quantities of aerosols. Perhaps the addition of MMT and the removal of aromatics would decrease aerosol formation and improve visibility.

It must be emphasized that these conclusions are based on very limited studies, which assumed that xylenes would be added to gasoline to increase its octane rating. Xylenes are known to be photochemically reactive. If other octane enhancers less photochemically reactive (e.g., MTBE or ETBE) had been used in the modeling efforts, the relative benefit, if any, of MMT on ozone formation would be reduced.

References

1. Calspan Corporation, "A Methodology for Determining the Effects of Fuel and Additives Combustion Products on Atmospheric Visibility." Draft Final Report to EPA Contract 68-02-0698 (1975).

2. Finlayson-Pitts, B. J. and J. N. Pitts, Jr., Atmospheric Chemistry: Fundamentals and Experimental Techniques, John Wiley and Sons, New York,NY 1986.

3. General Motors (1990), Private Communication to J. Bufalini.

4. Lurman, F., Evaluation of the Photochemical Reactivity of Emissions from Vehicles Using Fuels with the HITEC 3000 Additive", Letter to Ethyl Chemical Group, July 12, 1990.

5. Systems Application Inc., "Appendix 5: Use of the Urban Airshed Model to Assess the Effects of HITEC 3000 Performance Additive on Urban Air Quality," Report to Ethyl Petroleum Additives, Inc., May 4, 1990.

Attachment 7

EFFECTS OF MMT ON THE GREENHOUSE GAS INVENTORY

This attachment presents an analysis, prepared by ORD's Office of Environmental Processes and Effects (OEPER), of the effect that the introduction of MMT in gasoline would be expected to have on the greenhouse gas inventory. The issue is of interest, because Ethyl predicts that use of MMT will mean less fossil fuel energy will be needed in the refinement of gasoline.

Analysis

In its waiver application (see page 70 of the May 9, 1990 Waiver Request), Ethyl claims that "the additive could result in a reduction in crude oil imports of about 30 million barrels per year," presumably because refineries will need less cracking/reforming energy due to the reduced requirement for aromatics in finished gasoline.

Assuming that (1) the 30 million barrel per year figure is accurate, and (2) this savings can be totally realized as a carbon dioxide reduction, then

$$30 \text{ mill. bbl/yr} \times 42 \text{ gal/bbl} \times 7 \text{ lbs/gal}^{1} \times 1 \text{ ton/2000 lbs} \times 0.78 \text{ ton } CO_2\text{/ton oil}^{2}$$
$$= 3.44 \text{ million tons } CO_2\text{/yr saved} = 0.93 \text{ mill. tons C/yr}$$

This CO_2 savings of 3.44×10^6 tons CO_2 or 0.93×10^6 tons C must be offset by the apparent slight increase in methane emissions from automobiles due to MMT use. If one "averages" the "with" and "without" MMT tailpipe emissions presented in the waiver appendix, the rough increase is about 20 mg methane/mile. (Note that the uncertainty of this estimate is very large, because (1) the available test data are sparse and (2) the estimate was obtained from the small difference between two large numbers.)

Assuming the U.S. drives approximately 2×10^{12} mi/yr (frequently cited number in 1990 reports as of 1987), increased methane emissions due to MMT would be:

$$20 \text{ mg/mi} \times 2 \times 10^{12} \text{ mi/yr} \times 1 \text{ g/1000 mg} \times 1 \text{ lb/454 g} \times 1 \text{ ton/2000 lbs}$$
$$= 0.044 \times 10^6 \text{ tons methane/yr}$$

In terms of "radiative forcing power," methane is about 20-25 times more potent than CO_2. Methane CO_2 increase equivalents = $25 \times 0.044 \times 10^6 = 1.1 \times 10^6$ tons/yr.

Estimated net CO_2 savings due to MMT use = 3.44 - 1.10 =
2.3×10^6 tons/yr $CO_2 = 0.6 \times 10^6$ tons C/yr.

Interpretation of Results

- Current total U.S. fossil fuel emissions: 1230 million tons C/yr
- Current U.S. transportation emissions: 332 million tons C/yr
- MMT net estimated emissions savings: 0.6 million tons C/yr
- Estimated current crude oil inputs to U.S.: 8.5 million bbl/day
- Estimated crude oil input savings by MMT use: 3.5 days
- President's proposed minimum level tree planting program initiative for carbon sequestration: 9 increasing to 55 million tons C/yr (2000-2030)

ORD Conclusion

The introduction of MMT would result in negligible changes to the greenhouse gas inventory.

References

1. Mark's Standard Handbook for Mechanical Engineers, 8th edition, p. 7-14.

2. Marland, G. and Rotty, R., Tellus (1989), 36 B. p.232-261 p. 254, Table 14.

3. CDIAC (Carbon Dioxide Information Analysis Center) Communications, Spring 1990, p. 12. Carbon Dioxide Information Analysis Center, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

4. U.S. Environmental Protection Agency. Draft Report to Congress "Policy Options for Stablizing Global Climate," February 1989, p. 27-28.

Attachment 8

COMMENTS ON SELECTED COMMENTS RECEIVED IN THE DOCKET

This attachment provides ORD comments on specific comments received in the docket by the Ethyl Corporation and National Institute of Environmental Health Sciences. The comments of these groups are fairly inclusive of the comments received from other scientists and scientific organizations.

I. Ethyl Corporation Comments

Ethyl makes various arguments that there would be no health risks associated with the exposure to manganese (Mn) as a result of the introduction of MMT into unleaded gasoline. ORD's views concerning these issues are discussed below.

Ethyl considers daily intake by inhalation to be roughly toxicologically equivalent to oral ingestion, although Ethyl does use route-specific absorption factors. Indeed, inhalation presents a small contribution to the total mass uptake, given the high background oral dosage. However, the important issue is dose to the target tissue, not dose entering the entire body. Rather, the health effects following inhalation appear to be a more appropriate indicator of potential inhalation health risk. The effects of inhaled Mn cannot be understood if treated solely as a portion of total body dose. (See Attachment 1 for a more detailed discussion.)

The Ethyl exposure assessment only uses current ambient levels of Mn (0.04 mg/m^3) in its calculations. Ethyl ignores microenvironments in which levels will be higher. Ethyl correctly reports the conclusions of OAQPS that "ambient air concentrations of Mn" do not pose a significant health risk. However, this conclusion is based, as stated, on ambient air, without considering microenvironmental peak exposures that would be expected if MMT were added to gasoline.

Ethyl quotes two articles that conclude that Mn related to MMT usage would not cause health problems (Abbott, 1987; Cooper, 1984). Both articles, however, equate health effects with general ambient air, not microenvironments, and focus on effects observed in occupational studies, without considering the wider range of susceptibility that would be expected in the general public. For example, Cooper (1984) discusses the relationship between inhalation and oral exposure, quoting data showing the tissue doses can be higher after inhalation exposure compared to an equivalent oral exposure. Abbott (1987) uses respiratory and oral Mn absorption figures similar to those of ORD, thereby supporting the problems in directly equating inhalation and oral exposures. These papers do not conclude that inhalation exposures of Mn in microenvironments do not pose a potential risk.

Ethyl also concludes that exposure to MMT itself poses no health risk. ORD agrees that since MMT degrades so rapidly in the atmosphere and has such a low vapor pressure, evaporation would represent little to no inhalation public health risk. Elsewhere, in Attachment 5, ORD has commented on the oral exposure route through groundwater and bottom sediment.

Ethyl, on August 23, 1990, submitted additional comments, attempting to rebut many of the NIEHS comments (below), offering both specific quotations of the literature and general conclusions from the literature. Their general conclusions are a restatement of original positions in their petition. Generally, all parties agree that high levels of Mn can cause adverse health effects. Opinions diverge, however, on whether environmental levels will or will not cause a health risk. Ethyl reiterates its opinion that inhaled Mn_3O_4 (from MMT usage) will have an "infinitesimal effect on human manganese exposure." They are inconsistent in some interpretations of the literature which has numerous gaps. When NIEHS draws conclusions beyond the hard data, Ethyl correctly notes that extensive confirming data are not available (e.g., relationship of Mn neurotoxicity to dopamine depletion). However, Ethyl itself forms conclusions beyond hard data (e.g., percent Mn intake from inhalation) to support its positions. Ethyl obviously has made a significant effort to evaluate the literature. However, all of the issues they raised already have been considered by ORD.

II. National Institute of Environmental Health Sciences Comments

The National Institute of Environmental Health Sciences (NIEHS) placed a significant emphasis on the MMT dermal and oral accidental routes of exposure in their "statement," but not in their accompanying more detailed "General Discussion." ORD believes that although dermal and oral exposure to MMT might cause health effects, the risks of exposure to pure MMT are limited for oral exposure and even more limited for dermal exposure. The potential for acute dermal or oral exposure to MMT-gasoline mixtures is higher, since gasoline is used as a degreasing agent by some of the general public and there are a number of cases of accidental swallowing of gasoline by children. Both scenarios pose risk, especially for children. Although the data base is quite deficient for MMT-gasoline mixtures, ORD concludes that in these acute exposure scenarios, the toxicity from the gasoline itself is likely to pose a greater risk.

NIEHS raised a number of key issues, especially neurotoxicity, referencing the OHEA Mn document (1984), as well as individual papers. The key health endpoint of concern is neurological effects that have similar signs and symptoms to Parkinson's Disease. They also raise the important point of potential subclinical effects to the nervous system thought to represent a loss of reserve function, taking the position that this is an adverse response. Sensitive subpopulations are

identified, as is the potential for irreversible or long-term effects. NIEHS also discusses that individual susceptibility to Mn appears to vary.

ORD believes that all of these issues are being addressed in the form of the oral RfD or in the inhalation RfC for Mn. The RfC methodology requires review of the data base, selection of the critical paper for RfC derivation, and application of uncertainty factors and modifying factors to account for sensitive subpopulations and uncertainties in the data base.

ORD's only significant point of disagreement with the arguments presented by NIEHS regards the NIEHS view that several populations exist that have unique individual susceptibilities to manganese absorption. It is known that manganese absorption is dependent upon the same gastrointestinal transport mechanism as iron. One specific genetic aberration that could affect manganese absorption and, hence, manganese toxicity is that of idiopathic hemchromatosis (Cartwright, G. E. et al., "Hereditary hemochromatosis: Phenotypic expression of the disease," New Engl. J. Med. 301: 175-179 (1979)). The genotypic incidence is 5-6 in 1000 individuals with a phenotypic expression of about 3 in 1000. The affected individuals have abnormally high iron absorption that can lead to lethal accumulation of whole body iron. It is suggested by NIEHS that individuals, such as described above, are potentially at risk for excess manganese absorption and, hence, manganese toxicity. Furthermore, NIEHS hypothesizes that disruption in biliary function could interfere with the normal homeostatic mechanisms of manganese absorption and lead to a potentially toxic condition. While the theoretical situation for a condition of oral toxicity via ingestion does exist for manganese, it is not supported by the current literature. To date, oral manganese toxicity has not been reported in humans under normal circumstances for the general population or for particular populations as identified above. It is only under unique conditions that oral manganese toxicity has been reported, i.e., consumption of well water contaminated by manganese from a battery dump (Kawamura, R.H. et al., "Intoxication by manganese in well water, Kitasato Arch. Exp. Med. 18: 145-169 (1941)).

Other ORD comments follow:

(1) NIEHS's discussion of essential dietary requirements for Mn is virtually identical to ORD's.

(2) NIEHS questions the scientific validity of Ethyl's data concerning tailpipe emissions of Mn. ORD is also concerned about the paucity of Mn tailpipe emissions.

(3) NIEHS is concerned about soil deposition of Mn and subsequent ingestion of that soil by children. ORD's analysis (Attachment 4) indicates this does not appear to be a significant problem.

(4) NIEHS discusses the issue of human exposure to Mn qualitatively. ORD has performed an analysis of the inhalation exposure route and a less detailed analysis of potential oral exposures.